

EXHIBIT 1



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(54) **CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES**

(71) Applicant: **JAZZ PHARMACEUTICALS, INC.**,
Palo Alto, CA (US)

(72) Inventors: **Clark Allphin**, Seattle, WA (US);
James Pfeiffer, Palo Alto, CA (US)

(73) Assignee: **JAZZ PHARMACEUTICALS, INC.**,
Palo Alto, CA (US)

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(58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — Patricia Duffy

Assistant Examiner — Garen Gottfredson

(74) Attorney, Agent, or Firm — Cooley LLP

(57) **ABSTRACT**

Controlled release dosage forms are described herein. The controlled release formulations described herein provide prolonged delivery of high dose drugs that are highly water soluble and highly hygroscopic. In specific embodiments, controlled release dosage forms for delivery of a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. The controlled release dosage forms described herein may incorporate both controlled release and immediate release formulations in a single unit dosage form.

27 Claims, 9 Drawing Sheets

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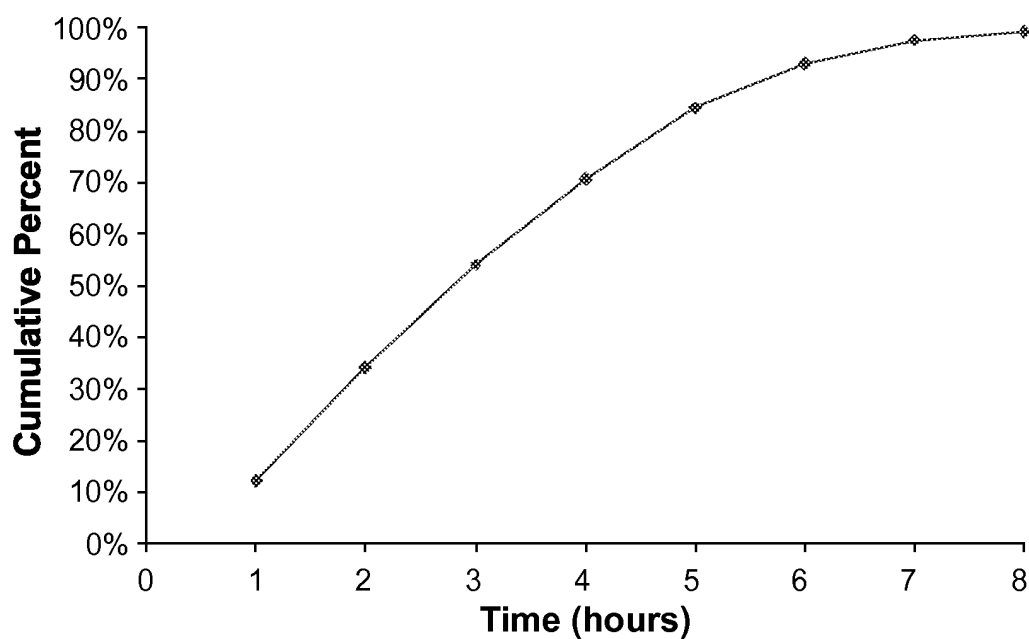


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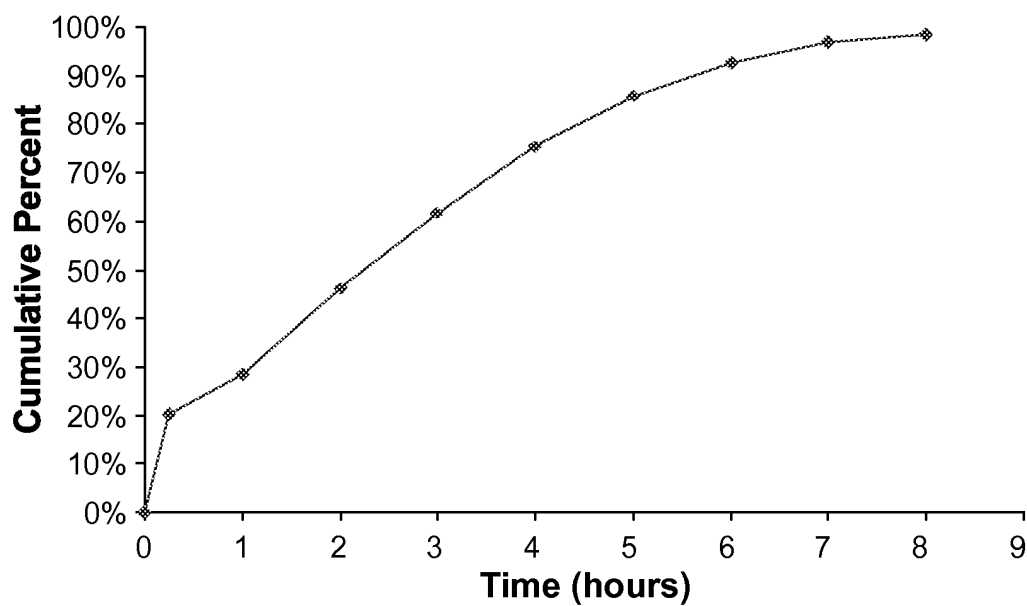


FIG. 2

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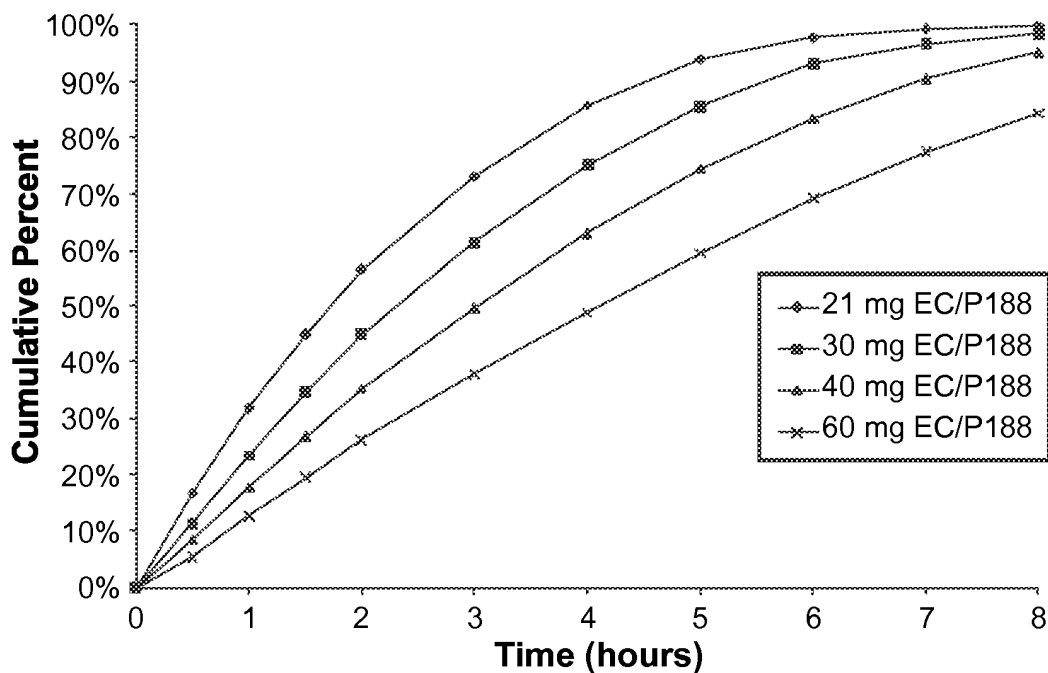


FIG. 3

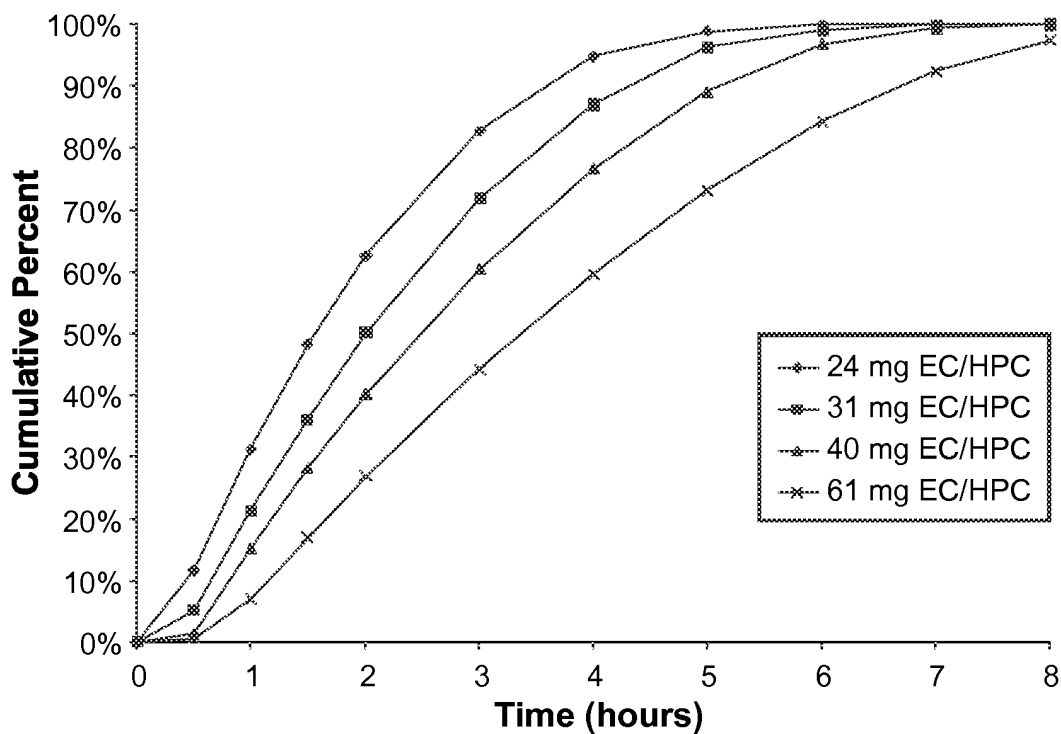


FIG. 4

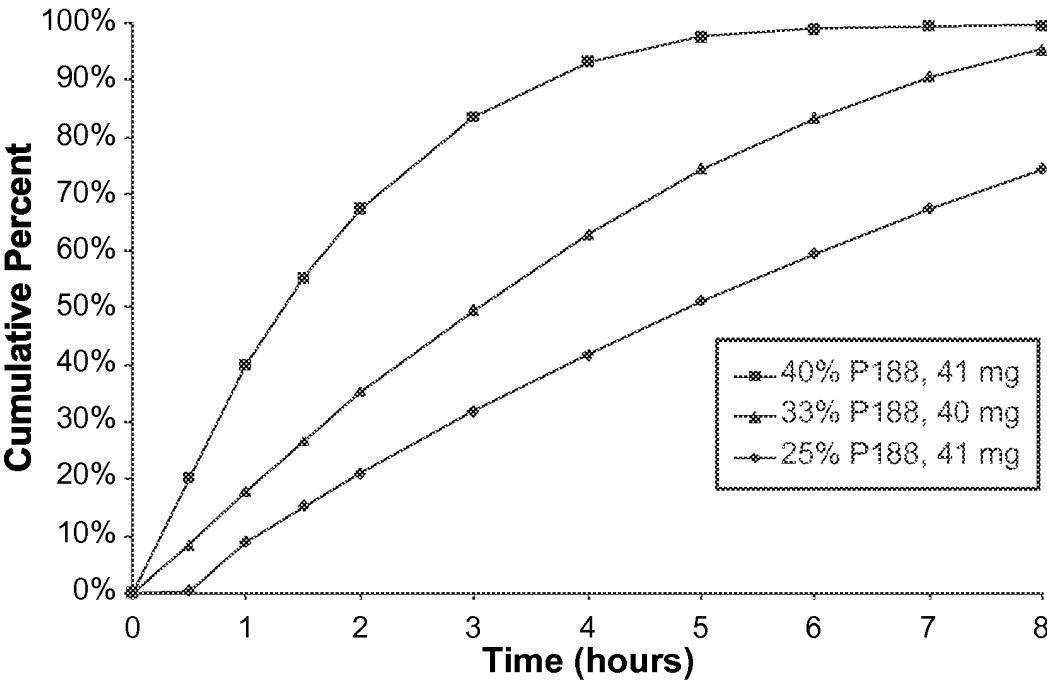


FIG. 5

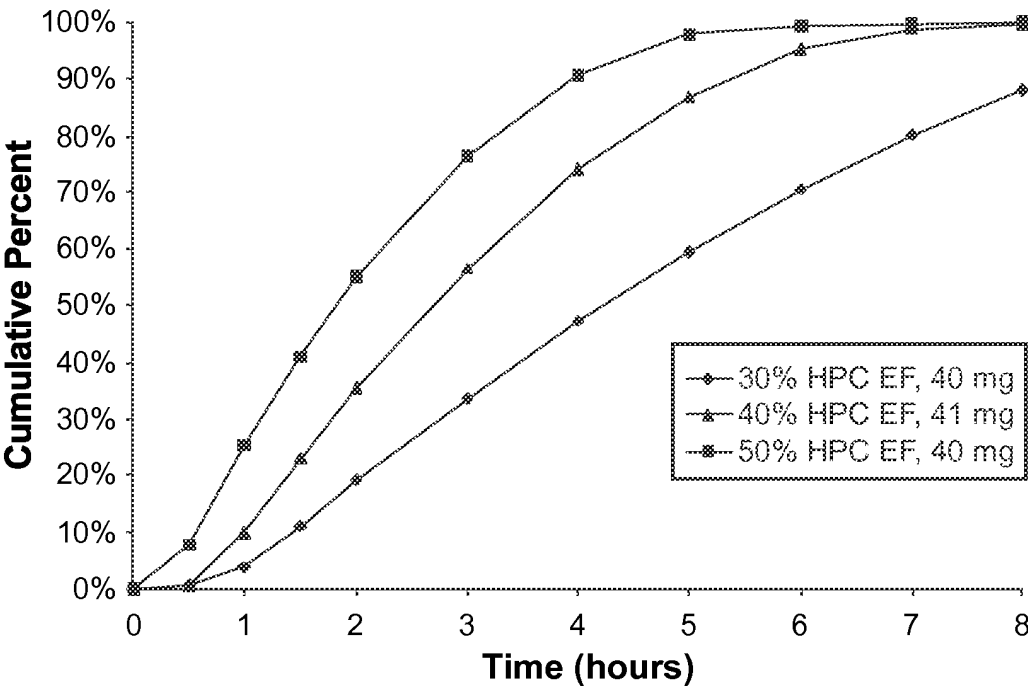


FIG. 6

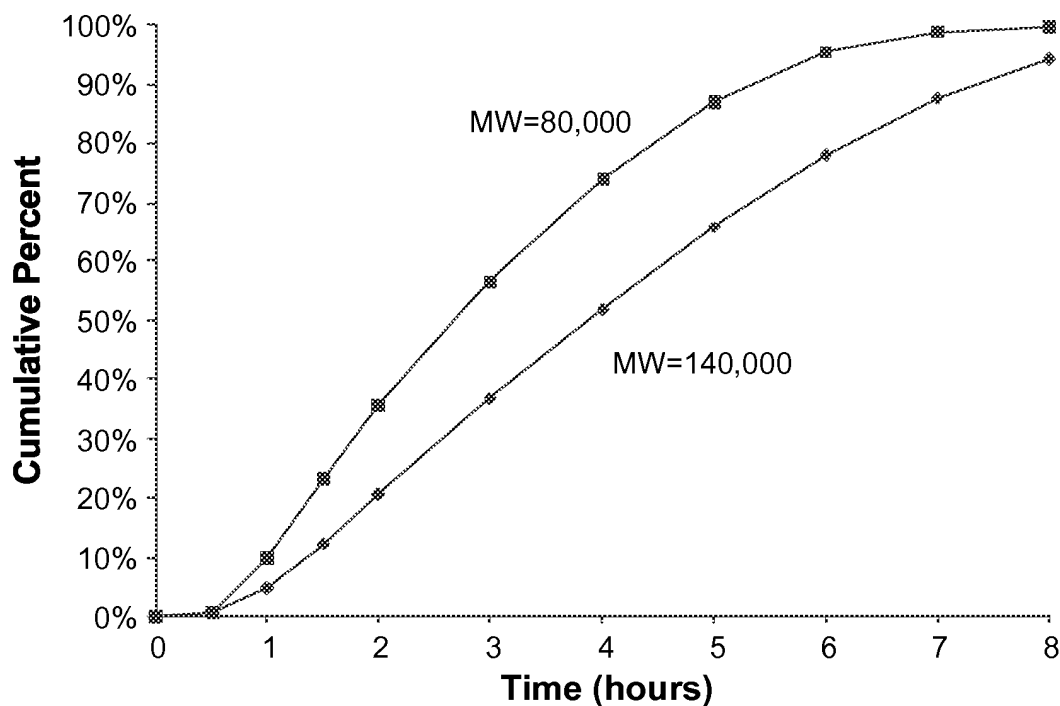


FIG. 7

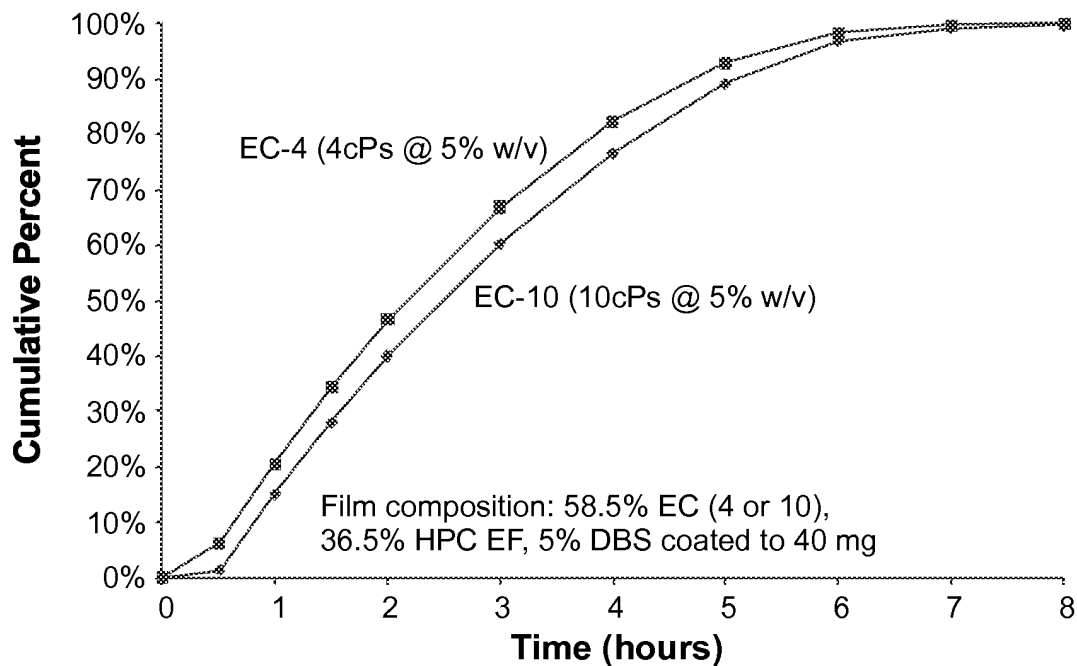


FIG. 8

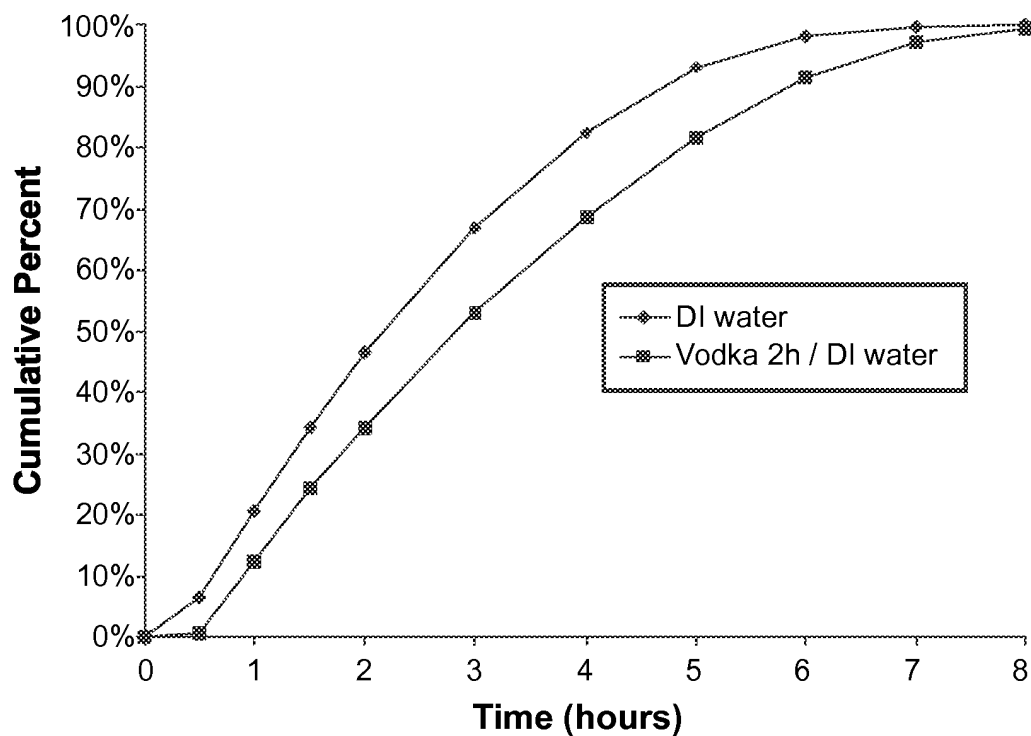


FIG. 9A

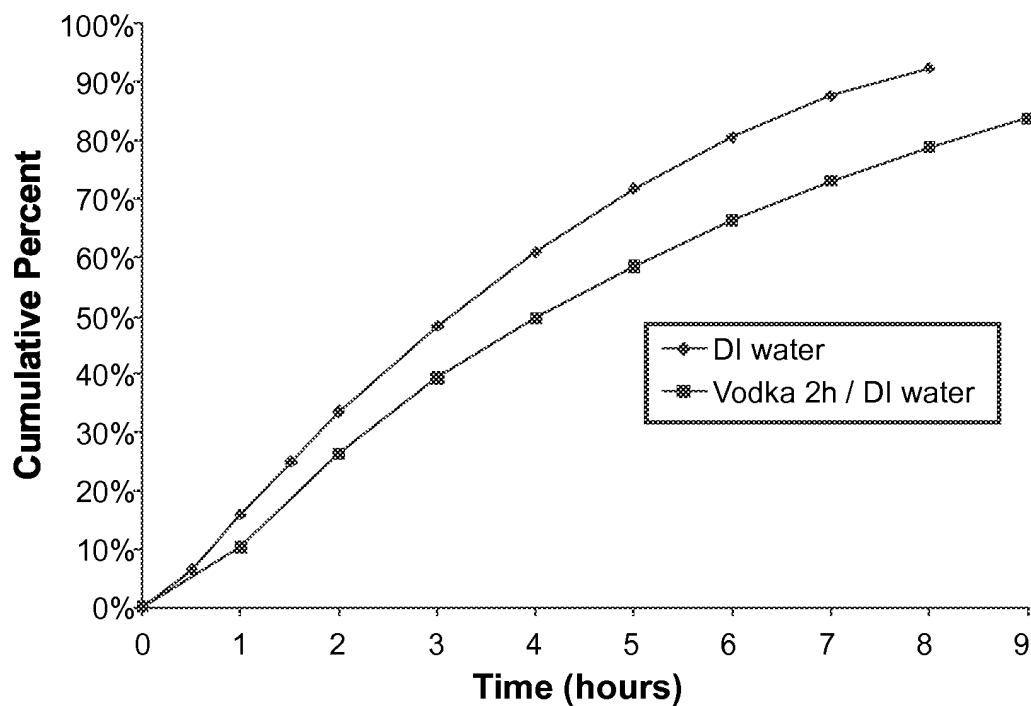


FIG. 9B

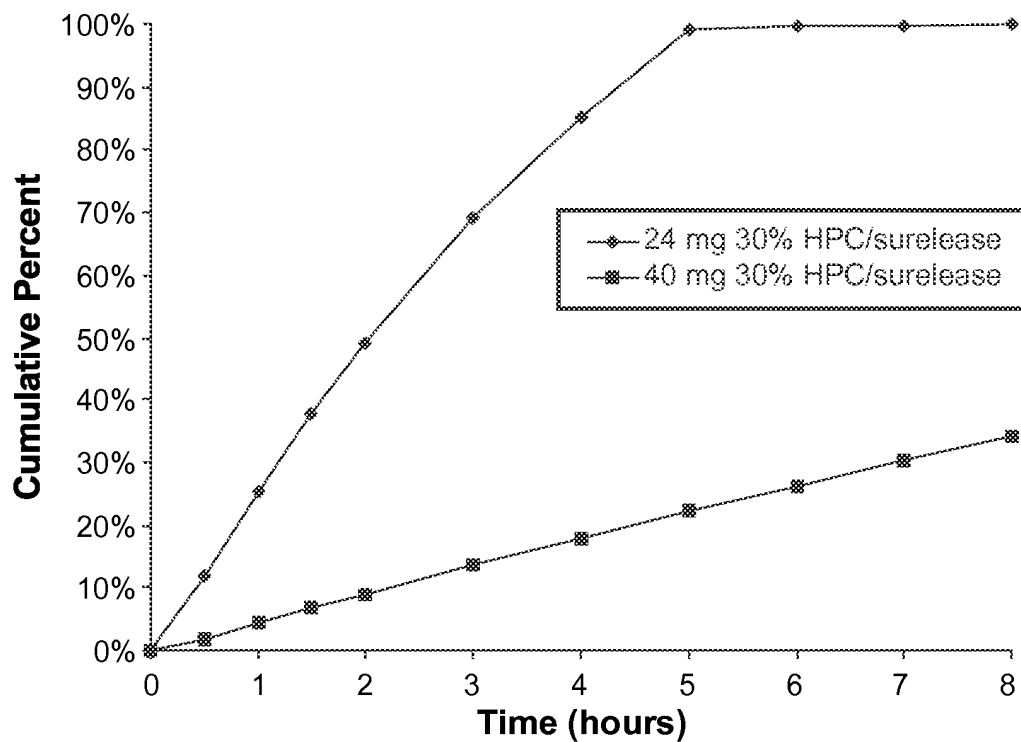


FIG. 10

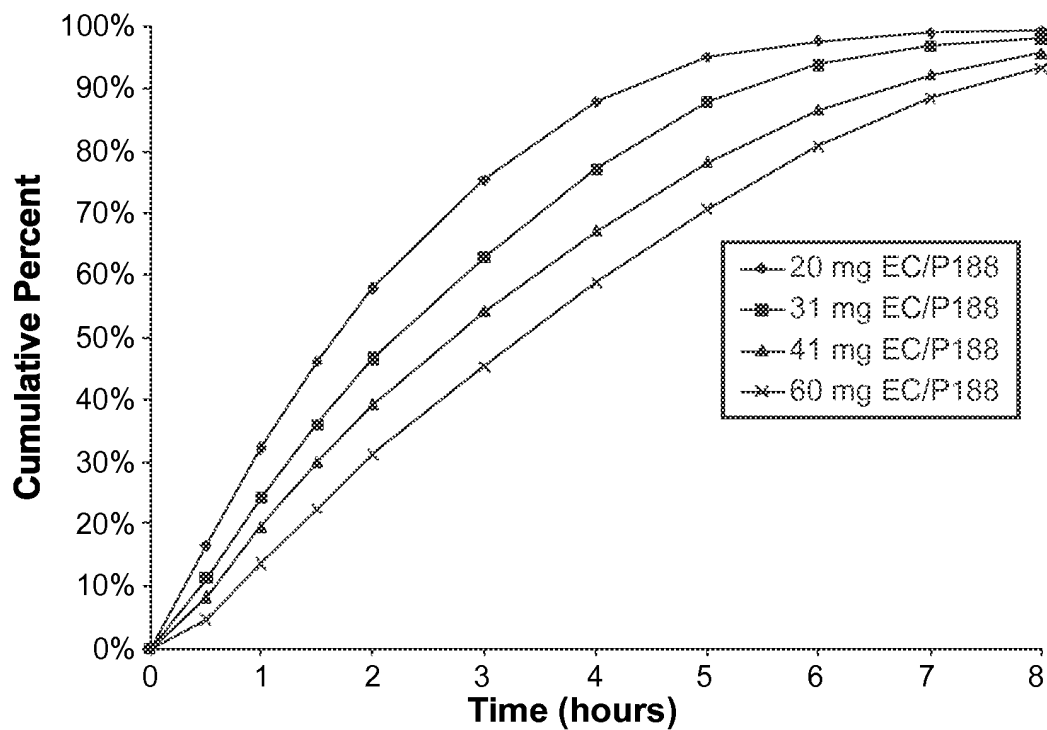


FIG. 11

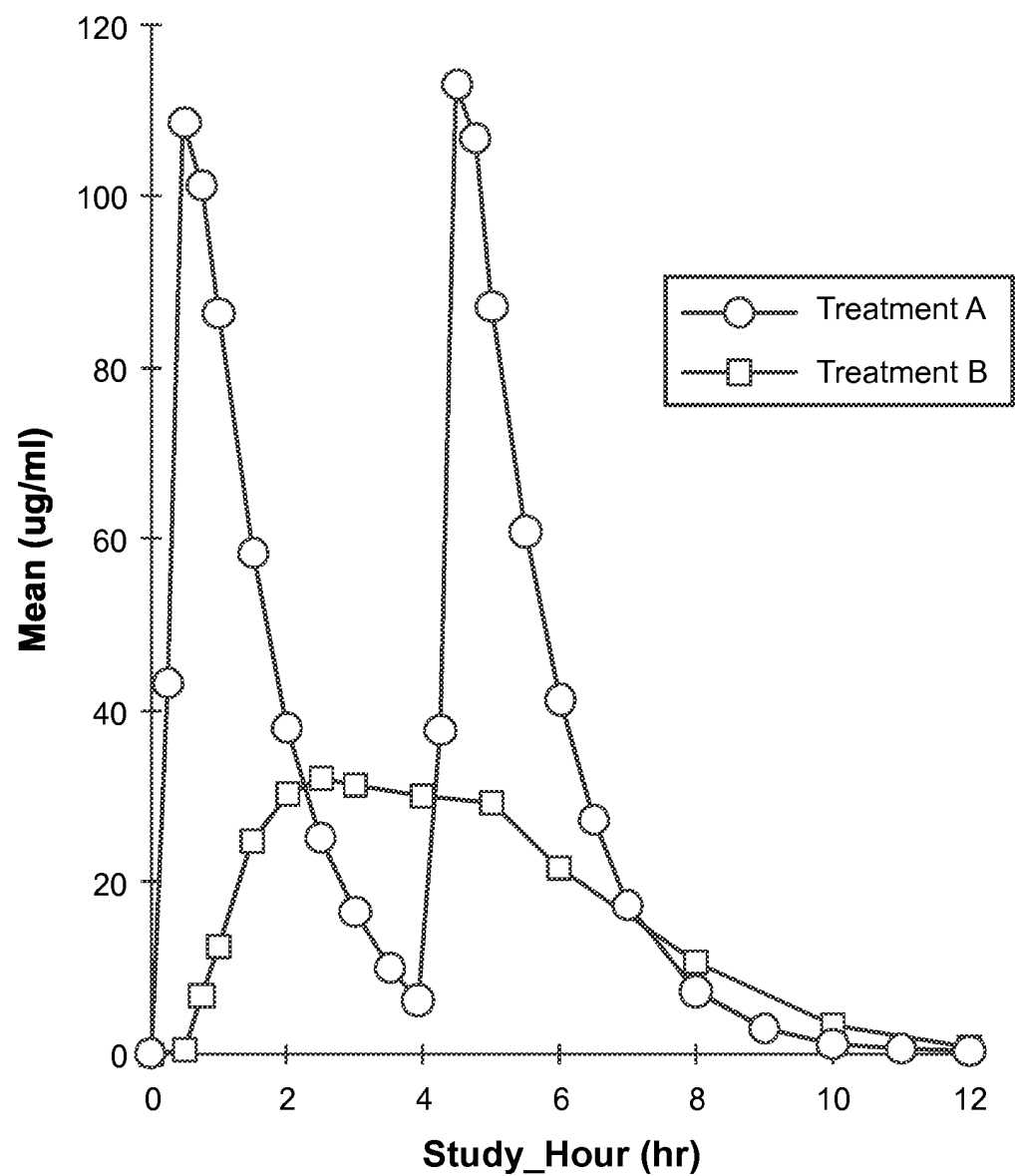


FIG. 12

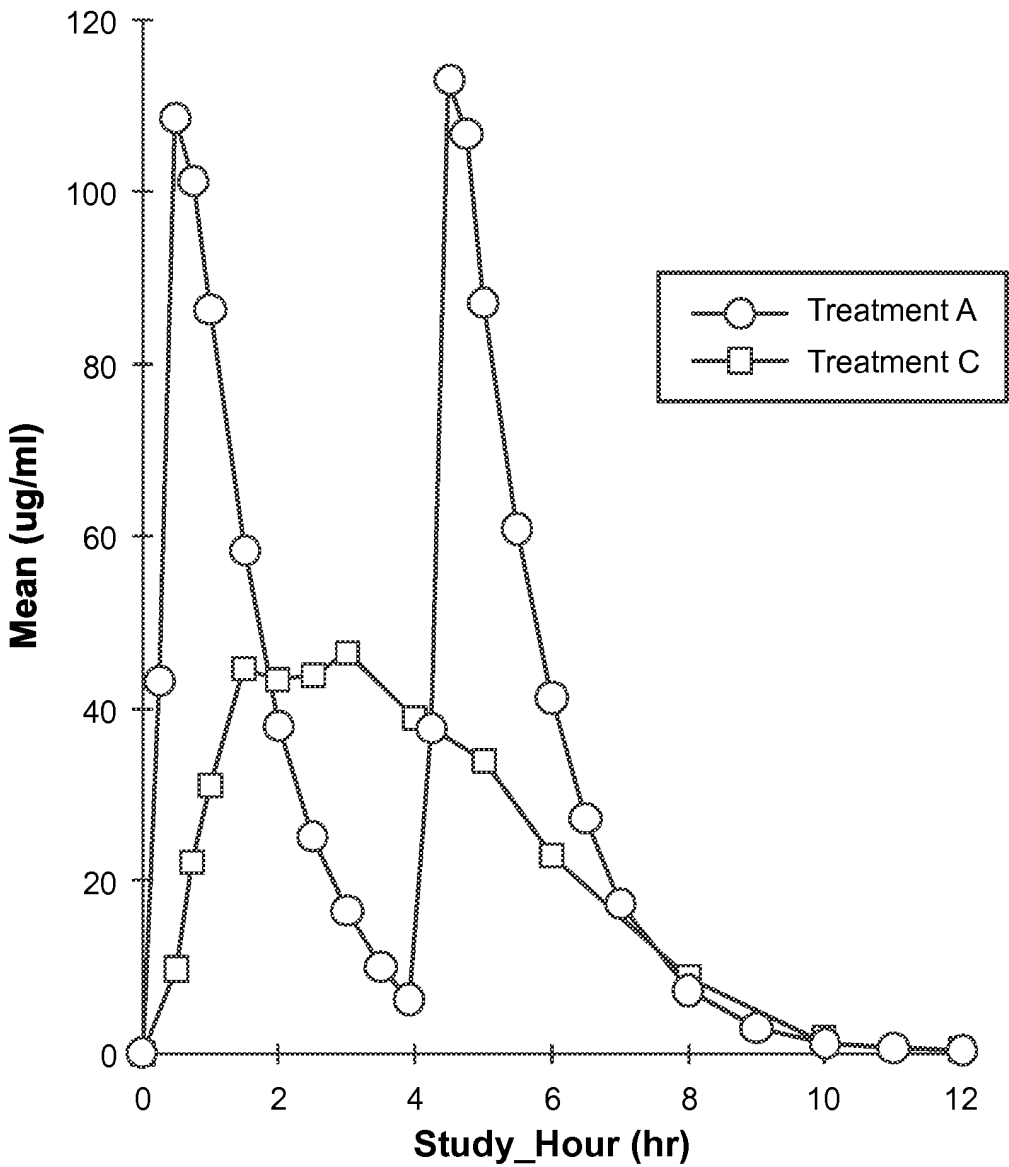


FIG. 13

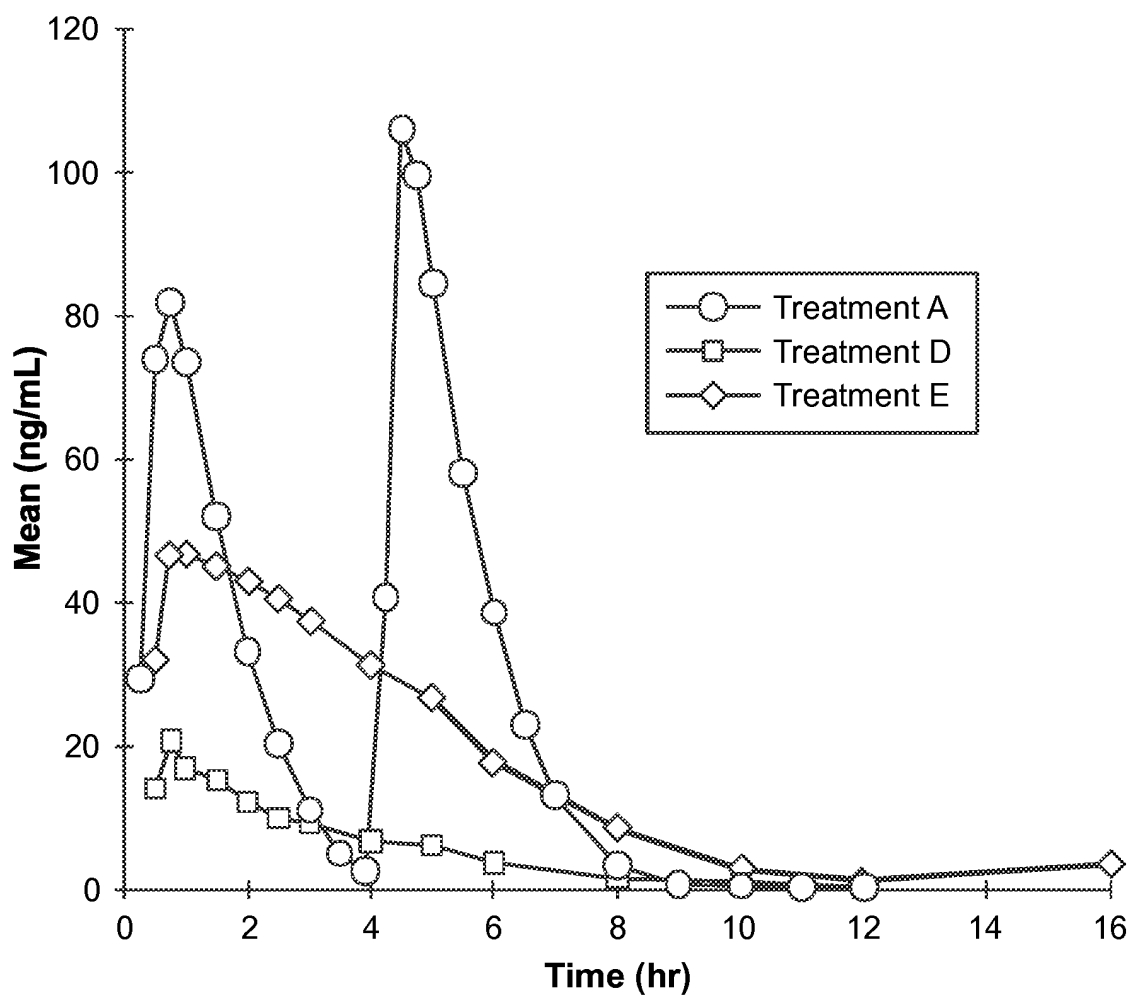


FIG. 14

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CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 16/916,677, filed Jun. 30, 2020, which is a continuation of U.S. patent application Ser. No. 16/712,260, filed Dec. 12, 2019, which is a continuation of U.S. patent application Ser. No. 16/025,487, filed Jul. 2, 2018, now U.S. Pat. No. 10,758,488, which is a continuation of U.S. patent application Ser. No. 13/071,369, filed Mar. 24, 2011, now abandoned, which claims the benefit of U.S. Provisional Application No. 61/317,212, filed on Mar. 24, 2010, the contents of each of which are incorporated herein by reference.

TECHNICAL FIELD

This disclosure relates to controlled release drug compositions.

BACKGROUND

For some drugs, it is difficult to formulate a controlled release dosage form that maintains an effective concentration of the drug over a sustained period of time. In particular, drugs that are administered at a high dose, drugs having a low molecular weight, and drugs with high water solubility make formulation of a controlled release dosage form challenging. For example, in the context of a controlled release drug formulation produced as a unit dosage form for oral administration, drugs that must be administered at a high dose constrain the amount of rate controlling excipients that can be used in formulating a drug composition that is both capable of sustained delivery of therapeutic doses of the drug and exhibits a size and shape suited to oral administration. Low molecular weight and high-solubility drugs may also readily permeate films and matrices that might otherwise be used to control release, and high solubility drugs are not suited to some drug delivery approaches, particularly where zero-order release kinetics are desired. An example of a drug that is administered at a high dose, has a low molecular weight, and high water solubility, is gamma-hydroxy butyrate (GHB), particularly the sodium salt of GHB.

Initial interest in the use of GHB as a potential treatment for narcolepsy arose from observations made during the use of GHB for anesthesia. Unlike traditional hypnotics, GHB induces sleep that closely resembles normal, physiologic sleep (Mamelak et al., *Biol Psych* 1977;12:273-288). Therefore, early investigators administered GHB to patients suffering from disorders of disturbed sleep, including narcolepsy (Broughton et al. in *Narcolepsy*, NY, NY: Spectrum Publications, Inc. 1976:659-668), where it was found to increase total nocturnal sleep time, decrease nocturnal awakenings and increase Stage 3-4 (slow wave) sleep. Three open-label and two placebo-controlled studies provided a body of evidence demonstrating that improvements in nocturnal sleep were associated with a reduction in cataplexy and improvements in excessive daytime sleepiness (Broughton et al., *Can J. Neurol Sci* 1979; 6:1-6, and Broughton et al., *Can J. Neurol Sci* 1980; 7:23-30).

An estimated 6 million Americans suffer the often baffling symptoms of fibromyalgia or chronic fatigue syndrome. Patients with fibromyalgia, also referred to as fibromyalgia

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syndrome, FMS or fibrositis syndrome, report widespread musculoskeletal pain, chronic fatigue, and non-restorative sleep. These patients show specific regions of localized tenderness in the absence of demonstrable anatomic or biochemical pathology, and patients suffering from fibromyalgia typically describe light and/or restless sleep, often reporting that they awaken feeling unrefreshed with pain, stiffness, physical exhaustion, and lethargy. See, H. D. Moldofsky et al., *J. Musculoskel. Pain*, 1, 49 (1993). In a series of studies, Moldofsky's group has shown that aspects of the patients' sleep pathology are related to their pain and mood symptoms. That is, patients with fibrositis syndrome show an alpha (7.5 to 11 Hz) electroencephalographic (EEG), non-rapid-eye-movement (NREM) sleep anomaly correlated with musculoskeletal pain and altered mood. Moldofsky has interpreted this alpha EEG NREM sleep anomaly to be an indicator of an arousal disorder within sleep associated with the subjective experience of non-restorative sleep. See H. D. Moldofsky et al., *Psychosom. Med.*, 37, 341 (1975).

Fibromyalgia patients frequently report symptoms similar to those of patients with post-infectious neuromyasthenia, also referred to as chronic fatigue syndrome (CFS). CFS is a debilitating disorder characterized by profound tiredness or fatigue. Patients with CFS may become exhausted with only light physical exertion. They often must function at a level of activity substantially lower than their capacity before the onset of illness. In addition to these key defining characteristics, patients generally report various nonspecific symptoms, including weakness, muscle aches and pains, excessive sleep, malaise, fever, sore throat, tender lymph nodes, impaired memory and/or mental concentration, insomnia, and depression. CFS can persist for years. Compared with fibromyalgia patients, chronic fatigue patients have similarly disordered sleep, localized tenderness, and complaints of diffuse pain and fatigue.

Scharf et al. conducted an open-label study to evaluate the effects of GHB on the sleep patterns and symptoms of non-narcoleptic patients with fibromyalgia (Scharf et al., *J Rheumatol* 1998; 25: 1986-1990). Eleven patients with previously confirmed diagnosis of fibromyalgia who reported at least a 3-month history of widespread musculoskeletal pain in all body quadrants and tenderness in a least 5 specific trigger point sites participated in the study. Results showed that patients reported significant improvements in the subjective assessments of their levels of pain and fatigue over all 4 weeks of GHB treatment as compared to baseline, as well as a significant improvement in their estimates of overall wellness before and after GHB treatment.

WO 2006/053186 to Frucht describes an open label study of 5 patients with hyperkinetic movement disorders including ethanol responsive myoclonus and essential tremor. Sodium oxybate, a sodium salt of GHB, was reported to produce dose-dependent improvements in blinded ratings of ethanol responsive myoclonus and tremor and was said to be tolerated at doses that provided clinical benefit.

XYREM® sodium oxybate oral solution, the FDA approved treatment for cataplexy and excessive daytime sleepiness associated with narcolepsy, contains 500 mg sodium oxybate/ml water, adjusted to pH=7.5 with malic acid. In man, the plasma half-life of sodium oxybate given orally is about 45 minutes and doses of 2.25 grams to 4.5 grams induce about 2 to 3 hours of sleep (See, L. Borgen et al., *J. Clin. Pharmacol.*, 40, 1053 (2000)). Due to the high doses required and very short half-life of sodium oxybate, optimal clinical effectiveness in narcolepsy typically requires dosing of the drug twice during the night, with

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administration typically recommended at 2.5 to 4 hour intervals. For each dose, a measured amount of the oral solution is removed from the primary container and transferred to a separate container where it is diluted with water before administration. The second dose is prepared at bed-

time and stored for administration during the night. Liang et al. (published U.S. patent application US 2006/0210630 A1) disclose administration of GHB using an immediate release component and a delayed release component. The delayed release component of the formulations taught in Liang et al., however, function in a pH dependent manner.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the delivery profile of sodium oxybate controlled release formulations as described herein.

FIG. 2 shows the delivery profile of integrated dosage forms as described herein having an immediate release component and a controlled release component.

FIG. 3 provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the coating weight of a functional coating.

FIG. 4 provides a graph further illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the coating weight of a functional coating.

FIG. 5 provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the amount of pore former included within a functional coating.

FIG. 6 provides a graph further illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the amount of pore former included within a functional coating.

FIG. 7 provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by varying the molecular weight of a pore former included within a functional coating.

FIG. 8 provides a graph illustrating that suitable controlled release profiles from dosage forms prepared according to the present description can be achieved even with functional coatings formed using different grades of the same base polymer material.

FIG. 9A and FIG. 9B provide graphs illustrating the effects of alcohol on the delivery profile of sustained-release formulations prepared as described herein.

FIG. 10 provides a graph illustrating the controlled release performance achieved by dosage forms as described herein having functional coatings prepared from aqueous dispersions of ethylcellulose as the base polymer.

FIG. 11 provides a graph illustrating the controlled release performance achieved by dosage forms as described herein incorporating calcium oxybate as the drug.

FIG. 12 provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein (Treatment B).

FIG. 13 provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein (Treatment C).

FIG. 14. provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium

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oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein dosed at 4 g (Treatment D) and 8 g (Treatment E).

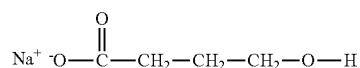
DETAILED DESCRIPTION

Formulations and dosage forms for the controlled release of a drug are described herein. Formulations described herein are suited to the controlled release of high dose drugs that are highly water soluble. In addition, in certain embodiments, the formulations described herein provide controlled release of drugs that are highly hygroscopic, even where such drugs must be administered at relatively high doses. In particular embodiments, the controlled release formulations are provided as a unit dosage form, and in one such embodiment, the controlled release formulation is provided as a coated tablet.

The formulations and dosage forms of the present invention can also include an immediate release component. The immediate release component can form part of a controlled release (CR) unit dosage form or may be a separate immediate release composition. Therefore, an immediate release (IR) component may be provided, for example, as a dry powder formulation, an immediate release tablet, an encapsulated formulation, or a liquid solution or suspension. However, the IR component may also be formulated as part of a single dosage form that integrates both the IR and CR components. In such an embodiment, the pharmaceutical formulation may be provided in the form of the coated tablet or capsule.

In specific embodiments, controlled release and immediate release formulations can be dosed together to a subject to provide quick onset of action, followed by maintenance of therapeutic levels of the drug substance over a sustained period of time. However, because the controlled release component and immediate release component described herein need not be present in a single dosage form, as it is used herein, the phrase "dosed together" refers to substantially simultaneous dosing of the controlled release and immediate release components, but not necessarily administration in the same dosage form. Dosing the controlled release and immediate release components together offers increased convenience, allowing patients to quickly achieve and maintain therapeutic levels of a drug over a sustained period of time, while reducing the frequency with which the drug must be dosed. Furthermore, dosing the controlled release and immediate release components together may avoid the disadvantages of dosing regimens and formulations that result in highly pulsatile plasma concentrations.

An example of a drug that may be used with the controlled release dosage forms described herein is GHB. It should be noted that embodiments of controlled release dosage forms comprising GHB, and other drugs, are presented herein for purposes of example only and not for purposes of limitation. The formulations and unit dosage forms provided herein can be utilized to achieve controlled release of GHB, as well as pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. Suitable salts of GHB include the calcium, lithium, potassium, sodium and magnesium salts. The structure of the sodium salt of GHB, sodium oxybate, is given as formula (I):



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Methods of making GHB salts are described, for example, in U.S. Pat. No. 4,393,236, which is incorporated herein by reference.

Formulating GHB into a unit dosage form presents various challenges, and such challenges are magnified in the context of formulating a unit dosage form providing controlled release of GHB. For instance, GHB is very soluble, generally requires a relatively high dose, has a low molecular weight, and exhibits a short circulating half-life once administered. Therefore, a controlled release unit dosage form of GHB should be configured to deliver large doses of drug over a prolonged period of time, while being acceptably sized for oral administration. However, controlled release formulations typically require the addition of significant amounts of excipients or rate controlling materials to control the delivery of drug, and the presence and need for such materials often limits the drug loading available for a given controlled release technology. Additionally, low molecular weight drugs, such as GHB, typically exhibit high permeability through films and matrices. Even further, high water solubility increases drug mobility and may preclude the use of some approaches utilized to achieved a controlled release dosage form.

Another challenge to achieving a formulation capable of delivering GHB over a sustained period of time is the fact that some forms of GHB, such as the sodium salt of GHB, sodium oxybate, are extremely hygroscopic. As used herein, the term "hygroscopic" is used to describe a substance that readily absorbs and attracts water from the surrounding environment. The hygroscopic nature of sodium oxybate presents significant challenges to the formulation, production, and storage of dosage forms capable of delivering sodium oxybate over a sustained period of time. Despite the challenges noted, formulations and unit dosage forms providing controlled release of GHB are described herein.

A. Controlled Release Formulations

As used herein, the term "controlled release" describes a formulation, such as, for example, a unit dosage form, that releases drug over a prolonged period of time. The controlled release compositions described herein may be provided as a unit dosage form suitable for oral administration. In each embodiment of the controlled release compositions described herein, the drug incorporated in such compositions may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB.

In certain embodiments, the controlled release compositions described herein are formulated as unit dosage forms that deliver therapeutically effective amounts of drug over a period of at least 4 hours. For example, controlled release unit dosage forms as described herein may be formulated to deliver therapeutically effective amounts of drug over a period selected from about 4 to about 12 hours. In specific embodiments, the controlled release dosage forms described herein deliver therapeutically effective amounts of drug over a period selected from about 4, about 5, about 6, about 7, about 8, about 9, about 10 hours, and about 12 hours. In other such embodiments, the controlled release dosage forms deliver therapeutically effective amounts of drug over a period selected from a range of about 4 to about 10 hours, about 5 to about 10 hours, about 5 to about 12 hours, about 6 to about 10 hours, about 6 to about 12 hours, about 7 to about 10 hours, about 7 to about 12 hours, about 8 to about 10 hours, and from about 8 to about 12 hours. In yet other embodiments, the controlled release dosage forms deliver therapeutically effective amounts of drug over a period selected from a range of about 5 to about 9 hours, about 5

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to about 8 hours, about 5 to about 7 hours, and about 6 to about 10 hours, about 6 to about 9 hours, and about 6 to about 8 hours.

The compositions described herein facilitate production of controlled release dosage forms that provide a substantially constant drug release rate. In one embodiment, the controlled release dosage forms may be formulated to deliver not more than approximately 30% of the drug initially contained within the controlled release dosage form in the first hour post-administration. When referencing the amount of drug initially contained in the controlled release dosage form or "initial drug content" of the controlled release dosage form, for purposes of the present description, such amount refers to the total amount of drug included in the controlled release composition prior to administration to a patient.

As is detailed herein, the controlled release dosage forms according to the present description include a controlled release component (also referred to as a controlled release "formulation") and, optionally, an immediate release component (also referred to as an immediate release "formulation" or an immediate release "coating"). In specific embodiments, the controlled release dosage forms described herein may be formulated to deliver drug to the gastro-intestinal tract at desired rates of release or release profiles. For example, in some embodiments, controlled release dosage forms as described herein are formulated to release to the gastro-intestinal tract not more than about 10% to about 60% of the drug initially contained within the controlled release component of the controlled release dosage form during the first two hours post-administration, and not more than about 40% to about 90% of the drug initially contained within the controlled release component of the controlled release dosage form during the first four hours post-administration. In other embodiments, controlled release dosage forms as described herein are formulated to release to the gastro-intestinal tract not more than about 40% of the drug initially contained within the controlled release component in the first hour post-administration, not more than about 60% of the drug initially contained within the controlled release component during the first two hours post-administration, and not more than about 90% of the drug initially contained within the controlled release component during the first four hours post-administration. In still other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 30% of the initial drug content in the controlled release component in the first hour post-administration, not more than about 60% of the initial drug content in the controlled release component during the first two hours post-administration, and not more than about 90% of the initial drug content of the controlled release component during the first four hours post-administration. In other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 50% of the initial drug content of the controlled release component during the first hour post-administration, between about 50 and about 75% of the initial drug content of the controlled release component after two hours, and not less than 80% of the initial drug content of the controlled release component after four hours post administration. In still other embodiments, a controlled release dosage form as described herein may be formulated release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component during the first hour post-administration, between about 5 and about 30% of the initial drug content of the controlled

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release component after two hours, between about 30% and about 50% of the initial drug content of the controlled release component after 4 hours, between about 50% and about 70% of the initial drug content of the controlled release component after 6 hours, and not less than about 80% of the initial drug content of the controlled release component after 10 hours post administration. In yet other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component after the first hour post-administration, between about 20% and about 50% of the initial drug content of the controlled release component after 2 hours, between about 50% and about 80% of the initial drug content of the controlled release component after 4 hours, and not less than 85% of the initial drug content of the controlled release component after 8 hours post-administration. The rate and extent of the absorption of GHB varies along the length of the GI tract with lower amounts absorbed in the more distal portions (i.e., the ileum and the colon).

Due to the rapid clearance of GHB from the plasma, when GHB is administered in an immediate release formulation, even large doses of the drug (e.g., a dose of between about 2.25 g and 4.5 g) generally result in plasma levels below 10 µg/mL within 4 hours of ingestion. In order to achieve therapeutic efficacy, therefore, a second, equal, dose is often required within 4 hours after administration of the first dose, and some patients may require administration of a second as soon as 2.5 hours after administration of the first dose. In such an instance, in order to maintain therapeutic efficacy, 4.5 g to 9 g of drug must be administered to the patient in two separate doses within 2 to 5 hours. This also requires that the second dose be administered during the night, which requires that the patient be awakened to take the second dose. The result is that the C_{max}/C_{min} ratio of GHB over an six hour period can be greater than 4 and is often greater than 8. In certain embodiments, for a given dose of GHB, administration of GHB using controlled release dosage forms as described herein can achieve a rapid rise in plasma concentrations of GHB, but with a prolonged duration of plasma levels above 10 µg/mL. In certain such embodiments, a GHB controlled release dosage form as described herein provides a C_{max} to C_{min} ratio of GHB over a prolonged period of time after administration selected from less than 3 and less than 2. Therefore, in specific embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a C_{max} to C_{min} ratio of GHB selected from less than 3 and less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours. For example, in particular embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a C_{max} to C_{min} ratio of GHB selected from less than 3 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours, while also providing GHB plasma concentrations of at least 10 µg/mL over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours. In still other embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a C_{max} to C_{min} ratio of GHB selected from less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours, while

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also providing GHB plasma concentrations of at least 10 µg/mL over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours.

Drug delivery performance provided by the dosage forms described herein can be evaluated using a standard USP type 2 or USP type 7 dissolution apparatus set to 37° C. ± 2° C. under the conditions described, for example, in the experimental examples provided herein. The dissolution media may be selected from dissolution media known by those of skill in the art such as at least one of purified water, 0.1N HCl, simulated intestinal fluid, and others.

In particular embodiments, the controlled release formulations described herein work to reduce inter patient variability in delivery of GHB. In particular, controlled release formulations described herein provide time dependent release of GHB over a sustained period of time. Previous references have described targeted release dosage forms of GHB that function in a pH dependent manner. However, due to inter-subject variability in gastrointestinal pH conditions, delivery of GHB from such dosage forms can be inconsistent. Moreover, because relatively high doses of GHB are typically required for therapeutic effect, unit dosage forms of GHB are also relatively large and may be retained for a period of time in the stomach, which can lead to intra- and inter-patient variability in dose delivery of GHB from pH dependent delivery systems due to variability in gastric retention time. Further, patients with fibromyalgia have an increased chance of also suffering from irritable bowel syndrome (see, e.g., *Fibromyalgia in patients with irritable bowel syndrome*. An association with the severity of the intestinal disorder, *Int J Colorectal Dis.* 2001 August; 16(4): 211-5.) Irritable bowel syndrome is also associated with delayed gastric emptying and variable gastric emptying (see, e.g., *Dyspepsia and its overlap with irritable bowel syndrome*, *Curr Gastroenterol Rep.* 2006 August; 8(4):266-72.) Therefore many patients with fibromyalgia and suffering from irritable bowel syndrome may experience more variability in gastric transit or prolonged gastric transit. By operating in a time dependent manner once placed in an aqueous environment, controlled release formulations described herein offer consistent GHB delivery characteristics and reduce the likelihood of undesirable intra- and inter-patient inconsistencies in dose delivery that may result from variances in gastric retention time that can occur between different patients and different patient populations.

Controlled release formulations described herein may be formulated to completely release a drug within a desired time interval. As has been reported, the bioavailability of GHB decreases in the lower GI, with bioavailability decreasing the lower the drug is delivered in the GI (See, e.g., U.S. Patent Publication No. US2006/0210630). Therefore, in certain embodiments, the controlled release dosage forms are provided that deliver substantially all the GHB contained therein over a sustained period of time that is long enough to increase patient convenience, yet short enough to reduce dosing of GHB in the lower GI. In specific embodiments, controlled release GHB dosage forms are provided that deliver approximately 90% or more of the GHB contained within the controlled release formulation within about 4 to about 10 hours of administration. For example, dosage forms for the controlled release of GHB as described herein may be formulated to deliver approximately 90% or more of the drug included within the controlled release formulation within about 4, 5, 6, 7, 8, 9, 10, or 12 hours of administration. In one such embodiment, a dosage form for the sustained delivery of GHB according to the present descrip-

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tion is formulated to deliver more than 90% of the GHB included within the controlled release formulation within 12 hours post-administration. Such embodiments serve to not only provide controlled release of GHB, but they also work to deliver GHB where bioavailability is highest, which can also provide increased dose consistency.

The controlled release dosage forms described herein may comprise a relatively high concentration of drug that can, in some instances, harm a patient if the formulation releases the drug at a rate that is faster than the intended sustained rate. This rapid release of the drug is sometimes referred to as "dose dumping." To avoid this potential danger, certain embodiments of the controlled release dosage forms described herein may comprise formulations that are resistant to dose dumping. Some users may intentionally attempt to increase the drug release rate of the controlled release dosage form using alcohol (e.g., potential abusers may take the controlled release dosage form prior to, simultaneously with, or after consuming an alcoholic beverage or, alternatively, may seek to extract the drug from the controlled release dosage form by placing the dosage form in solution containing alcohol). Other users may take the dosage form with alcohol, not necessarily in a manner considered abuse of the drug or alcohol, but without regard for the potential risks of dose dumping or contraindication of the two substances. In one embodiment, a controlled release dosage form as disclosed herein may include a coating composition that is resistant to alcohol or that does not dissolve substantially faster in alcohol. In one such embodiment, the controlled release dosage form may comprise the drug sodium oxybate and include a coating composition including ethylcellulose that is resistant to dose dumping in alcohol. In another embodiment, the controlled release dosage form may include a coating composition that is resistant to dose dumping after administration. For example, the controlled release dosage form may include a coating composition that is resistant to dose dumping in the GI tract after being exposed to gastric fluid and intestinal fluid.

In certain embodiments, the controlled release formulations described herein are provided as a coated tablet composition having a controlled release core coated by a functional overcoat. The composition of the controlled release core provided in such embodiments facilitates high drug loading, thereby, rendering the coated tablet suitable for formulation and sustained delivery of drugs administered at high doses. The functional overcoat works to control delivery of drug from the controlled release core and maintain the structural integrity of the dosage form over time. In addition to the controlled release core and functional overcoat, the coated tablet composition as described herein may further include a moisture barrier or cosmetic coating disposed over the functional overcoat.

I. Controlled Release Component

Where the controlled release formulations described herein are formulated as a coated tablet having a controlled release core (CR core), the CR core includes at least one drug substance to be delivered from the controlled release dosage form. The drug included in the CR core may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. Examples of suitable salts of GHB include the calcium, lithium, potassium, sodium and magnesium salts. The CR core is formulated and configured to be suitable for oral administration. In one embodiment, coated tablets as described herein may be administered to provide a dose of GHB or a pharmaceutically acceptable salt, hydrate, tautomer, solvate or complex of GHB in a range of about 500

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mg to about 12 g of drug in one or more tablets. In particular embodiments, a CR core included in a controlled release dosage form according to the present description may include an amount of drug selected from about 100 mg to about 2,000 mg. In some such embodiments, the amount of drug included in the CR core may be selected from up to about 250 mg, 400 mg, 500 mg, 600 mg, 700 mg, 750 mg, 800 mg, 900 mg, 1,000 mg, 1,100 mg, 1,200 mg, 1,400 mg, 1,500 mg, 1,600 mg, 1,700 mg, 1,800 mg, 1,900 mg, and 2,000 mg. In certain such embodiments, the amount of drug included in a CR core as described herein may range from about 500 mg to about 2,000 mg, such as, for example, about 500 mg to 1,000 mg, about 600 mg to 1,000 mg, about 600 mg to 900 mg, about 600 mg to 800 mg, about 700 mg to 1,000 mg, about 700 mg to 900 mg and about 700 mg to 850 mg. In other such embodiments, the amount of drug included in a CR core as described herein may range from about 700 mg to about 2,000 mg, such as, for example, about 700 mg to 1,500 mg, about 700 mg to 1,400 mg, about 700 mg to 1,300 mg, about 700 mg to 1,200 mg, about 700 mg to 1,100 mg, about 700 mg to 1,000 mg, about 700 mg to 900 mg, and about 700 mg to 850 mg.

In one embodiment, the controlled release dosage form comprises a CR core wherein the relative amount drug in the CR core is at least 90% or greater by weight. In another embodiment, the relative amount of drug in the CR core ranges from between about 90% and 98%, about 91% and 98%, about 92% and 98%, about 93% and 98%, about 94% and 98%, about 95% and 98%, about 96% and 98%, and between about 97% and 98% by weight of the CR core. In yet another embodiment, the relative amount of drug in a CR core may be present at an amount selected from about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, and 98% by weight of the CR core. In certain such embodiments, the amount of drug in the CR core may range from about 94 to 98%, 94 to 97%, 94 to 96%, 95 to 98%, 95 to 97%, and 95 to 96.5% by weight of the CR core.

In one embodiment, the controlled release dosage form comprises a CR core that includes drug substance in combination with one or more excipients, such as binders, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, lubricants, glidants, or other suitable excipients. In one embodiment, a CR core as disclosed herein can include one or more binders that are known for use in tablet formulations. In one such embodiment, a CR core may include at least one binder selected from hydroxypropyl cellulose (HPC), ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate. In specific embodiments, the CR core included in a controlled release dosage form as disclosed herein may comprise binder levels ranging from approximately 1% to 10% by weight. For example, the CR core may include a binder in an amount selected from about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, and 10% by weight. In certain such embodiments, the amount of binder included in the CR core may range from about 1 to 2%, 1 to 3%, 1 to 4%, 1 to 5%, 1 to 6%, 1 to 7%, 1 to 8%, 1 to 9% and 1 to 10% by weight.

The CR core may include one or more lubricants to improve desired processing characteristics. In one embodiment, the CR core may include one or more lubricants selected from at least one of magnesium stearate, stearic

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acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added to the CR core in a range of about 0.5% to 5% by weight. In particular embodiments, a CR core as disclosed herein may comprise a lubricant in a range of about 0.5% to 2% by weight, about 1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in the CR core in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight. Still lower lubricant levels may be achieved with use of a “puffer” system during tableting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation.

The CR core may also include one or more surfactants. In certain embodiments, the CR core may include a tableted composition that may comprise one or more surfactants selected from, for example, ionic and non-ionic surfactants. In one such embodiment, CR core may include at least one anionic surfactant, including docusate sodium (dioctyl sulfosuccinate sodium salt) and sodium lauryl sulfate. In yet another embodiment, the CR core may include at least one non-ionic surfactant selected from including polyoxyethylene alkyl ethers, polyoxyethylene stearates, poloxamers, polysorbate, sorbitan esters, and glyceryl monooleate. In specific embodiments, one or more surfactants included in a CR core as disclosed herein may be present, for example, in an amount of up to about 3.0% by weight of the CR core. For example, in certain embodiments, the CR core may include one or more surfactants present in a range selected from about 0.01% to 3%, about 0.01% to 2%, about 0.01% to 1%, about 0.5% to 3%, about 0.5% to 2%, and about 0.5% to 1% by weight of the CR core.

The CR core included in controlled release dosage form as disclosed herein may also include fillers or compression aids selected from at least one of lactose, calcium carbonate, calcium sulfate, compressible sugars, dextrates, dextrin, dextrose, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, powdered cellulose, and sucrose. In another embodiment, a CR core may be prepared by blending a drug and other excipients together, and the forming the blend into a tablet, caplet, pill, or other dosage form according to methods known by those of skill in the art. In certain embodiments, a controlled release formulation as described herein may comprise a solid oral dosage form of any desired shape and size including round, oval, oblong cylindrical, or triangular. In one such embodiment, the surfaces of the CR core may be flat, round, concave, or convex.

The CR core composition included in a controlled release formulation provided as a coated tablet dosage form as described herein may be manufactured using standard techniques, such as wet granulation, roller compaction, fluid bed granulation, and direct compression followed by compression on a conventional rotary tablet press as described in Remington, 20th edition, Chapter 45 (Oral Solid Dosage Forms).

II. Functional Coating Composition

Where the controlled release formulations as described herein are provided as a coated tablet composition, the CR core is coated with a functional coating. The coating composition works to preserve the integrity of the unit dosage form post administration and serves to facilitate controlled release of drug from the CR core. In certain embodiments,

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the coating composition is formulated to facilitate controlled release of a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. In one such embodiment, the coating composition is sufficiently robust to preserve the integrity of the coated tablet pre- and post-administration, yet is subject to disintegration or crushing as it passes through a patient’s gastrointestinal tract and after all or substantially all the drug substance contained within the controlled release formulation has been delivered. Such a feature reduces the risk that bezoars formed from intact dosage form shells will form or be maintained within the GI tract of a patient, which may be of particular concern where the drug to be delivered must be administered at high doses using multiple unit dosage forms.

In one embodiment, a functional coating composition as disclosed herein may control, at least in part, the rate of release of the drug to be delivered from the CR core into the gastrointestinal tract. In one embodiment, the functional coating composition provides a functional coat that partly or fully covers the CR core included in the controlled release dosage form. In one embodiment, the functional coating composition as disclosed herein may include a polymer or blends of compatible polymers that are water soluble or that are water insoluble and selected to exhibit desired permeability characteristics. In one embodiment, the functional coating composition has a permeability that may be adjusted according to the solubility of the drug used in the CR core. In one such embodiment, the functional coating composition may comprise one or more water insoluble polymers that may swell but do not substantially dissolve in the GI tract. For example, in particular embodiments, a functional coating composition as disclosed herein may comprise a rate-limiting film that includes at least one of ethylcellulose, cellulose acetate, such as CA-398. In other embodiments, the functional coating may include combinations of ethylcellulose with ammonio methacrylate copolymers, such as EUDRAGIT RS, EUDRAGIT RL, and combinations thereof. Suitable ethylcellulose materials are readily commercially available, and include, for example, ETHOCEL ethylcellulose polymers. Where ethylcellulose is used to form the functional coating, the physical characteristics of the coating composition and residual shell may be modified by adjusting the molecular weight of the ethylcellulose. For example, different grades of ethylcellulose, including, but not limited to, 4 cP, 7 cP, 10 cP, and 20 cP grades, may be used to achieve a coating composition having desired physical characteristics.

A functional coating composition as disclosed herein may include one or more base polymer and at least one pore-former. In one embodiment, the base polymer content may range from about 50% to about 80% by weight of the coating composition. In certain embodiments, the base polymer may be present in an amount ranging from about 50% to 75%, about 55% to 75%, about 60% to 75%, and about 65% to 75% by weight of the coating composition. In one such embodiment, the base polymer may be present in an amount selected from about 50%, 55%, 60%, 65%, 70%, 75%, and 80% by weight of the coating composition. In cases where a filler material is used (e.g., insoluble, non film-forming material such as magnesium stearate, talc, or fumed silica), these limits apply to the composition of the remaining non-filler components in the film.

The permeability of the base polymer included in a functional coating as described herein may be modified by including a pore former in the base polymer. In one such embodiment, the functional coating composition including the pore former may be obtained by combining the pore

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former with the base polymer material in solution according to conventional techniques. A pore former as disclosed herein may include at least one polymeric pore former, such as hydroxyalkyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycols, polyvinyl alcohol, povidone, copovidone, and poloxamers, such as 188 or 407. In one embodiment, a pore former as disclosed herein may include at least one small-molecule pore former, such as a water soluble sugar or organic acid, including, for example, citric acid or sorbitol. In one such embodiment, a small-molecule pore former may be water soluble active agent, such as a pharmaceutically acceptable salt of GHB. In yet another embodiment, the pore former may comprise a polymer that expands in the presence of the drug included in the CR core, wherein expansion of the pore former may cause an increase in permeability of the functional coating composition. For example, in some embodiments, the functional coating composition may comprise a pore former that that expands or swells in the presence of sodium oxybate. In one such embodiment, the pore former includes a suitable carbomer.

Where used in the functional coating composition, a pore former or a pore-forming agent can be selected to modify the permeability of the coating composition provided over the CR core. For example, the permeability of the functional coating composition may be increased by including one or more pore formers or pore-forming agents in the coating composition. In one embodiment, the pore formers disclosed herein may be soluble in water. In one such embodiment, when a CR dosage form comprising a functional coating composition with at least one pore former is swallowed by a patient and contacted with gastric fluid, the water-soluble pore formers may dissolve and form pores or channels in the coating through which the drug is released. It is possible to use an enteric component as part or all of the pore former in the coating composition. Examples of such materials that may be used as a pore former in the context of the present description include cellulose acetate phthalate, methacrylic acid-methyl methacrylate copolymers, and polyvinyl acetate phthalate. However, incorporating enteric components in the film may result in delivery characteristics that exhibit some level of sensitivity to gastric and intestinal transit times.

Where included, the amount and nature of the pore former included in the functional coating composition can be adjusted to obtain desired release rate characteristics for a given drug substance. In one embodiment, the functional coating composition may include an amount of pore former that ranges from about 20% to about 50% by weight of the coating composition. For example, the pore former may be present in an amount ranging from about 20% to 45%, about 25% to 45%, about 30% to 45%, and about 35% to 45% by weight of the functional coating composition. In one such embodiment, the pore former may be present in an amount selected from about 20%, 25%, 30%, 35%, 40%, 45%, and 50% by weight of the functional coating composition.

The functional coating composition as disclosed herein may also comprise one or more plasticizers. In certain embodiments, the functional coating composition may include a plasticizer such as triethyl citrate or dibutyl sebacate. In one such embodiment, a plasticizer may be present in the functional coating composition in an amount ranging from about 5% to 15% by weight relative to the base polymer. In certain embodiments, the functional coating composition may include a plasticizer in an amount selected from about 5%, 8%, 10%, 12%, and 15% by weight relative to the base polymer.

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The functional coating composition as disclosed herein may also include an anti-tack agent. For example, certain embodiments of the functional coating composition may include an anti-tack agent selected from one or more of talc, glyceryl monostearate, and magnesium stearate. Many of the anti-tack agents are also suitable fillers. Addition of fillers, especially magnesium stearate, is one way to make the film more brittle and the dosage form more prone to crushing as it transits through the GI. Depending on forces encountered in the GI, varying the filler level in the film may allow one to adjust the duration, or extent of drug delivered, at which breach of the film and abrupt release of remaining contents occurs.

The functional coating composition as disclosed herein may be applied to a CR core at a weight that facilitates a suitable combination of sustained drug release and dosage form structural integrity. In certain embodiments, the functional coating composition may be applied at a weight of about 10 to about 100 mg. In particular embodiments, for example, the functional coating may be applied at a weight selected from about 20 to 60 mg, about 20 to 50 mg, about 20 to 40 mg, about 20 to 30 mg, about 30 to 60 mg, about 30 to 50 mg, about 30 to 40 mg, about 40 to 60 mg, about 40 to 50 mg, and about 50 to 60 mg. These ranges are useful for oval tablets of about 500 mg to about 1000 mg in weight. Alternatively, for a given tablet size or weights, the functional coating composition as disclosed herein may be applied at between about 2.5% and 7.5% of the tablet weight. For example, in one such embodiment, where the tablet is a 2,000 mg oval tablet, a functional coating composition may be applied at a weight ranging from about 50 mg to about 150 mg.

In addition to adjusting the amount or nature of the pore former included in the functional coating composition, the release rate of drug provided by the controlled release dosage form disclosed herein may be adjusted by modifying the thickness or weight of the functional coating composition. For example, a more rapid release rate will generally be achieved as the amount of a given pore former included in the functional coating composition is increased or the thickness or weight of the coating composition applied over the CR core is decreased. Conversely, a slower or more controlled release may be achieved, generally, as relatively less of a given pore former is included in the functional coating composition or the thickness or weight of the coating composition applied to the CR core is increased. Additionally, in certain embodiments, the release rate of drug from the CR core may be adjusted by modifying the water content of the functional coating composition. For example, increasing the water content of the functional coating composition may increase the release rate of drug the CR core.

The functional coating compositions as disclosed herein may be applied to a CR core according to conventional coating methods and techniques. In one embodiment, the functional coating composition as disclosed herein may be applied using a conventional perforated pan coater. In another embodiment, the functional coating composition may be applied using an aqueous pan-coating process. In one such embodiment, the use of an aqueous pan-coating process may include the use of a latex dispersion. For example, a latex dispersion such as SURELEASE may be used for an ethylcellulose pan-coating process. In another example, a latex dispersion such as EUDRAGIT RS 30 D may be used in a pan-coating process for ammonio-methacrylates. In yet another embodiment, the functional coating composition may be applied using a solvent-based pan-coating process. In one such embodiment, a solvent-based

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pan-coating process may include the use of an alcohol solvent, such as ethanol. For example, an alcohol-solvent based pan-coating process may utilize a 95% ethanol and 5% water (w/w) solvent.

In one embodiment, the functional coating compositions as described herein may be applied using a fluid bed coating process such as a Wurster fluid bed film coating process. In another embodiment, the functional coating composition may be applied using a compression coating process. In yet another embodiment, the functional coating composition may be applied using a phase inversion process. In certain embodiments, the functional coating composition as disclosed herein may be applied over a suitable subcoating.

III. Moisture Barrier/Cosmetic Coatings

When a controlled release formulation or dosage form is provided as a coated tablet, in some embodiments, it may be coated with a moisture barrier or a moisture-resistant coating composition. For example, a controlled release dosage form as disclosed herein comprising GHB as the drug substance may include a moisture barrier. In another example, a moisture barrier may be particularly useful where sodium oxybate is used as the drug substance. In one embodiment, the moisture barrier may be a polyvinyl alcohol-based coating, such as OPADRY AMB (Colorcon Inc., Harleysville, Pa.). In another embodiment, the moisture barrier may be a hydroxypropyl methylcellulose (HPMC)/wax-based coating, such as AQUARIUS MG (Ashland Aqualon, Wilmington, Del.). In yet another embodiment, the moisture barrier may be a HPMC/stearic acid-based coating. The moisture barrier as disclosed herein, in some embodiments, may be formed using a reverse enteric material, such as EUDRAGIT E, and may be coated from alcohol or alcohol/water solutions or from an aqueous latex dispersion. In embodiments where the controlled release dosage form is provided as a tablet of about 500 mg-1000 mg in weight, for example, the moisture barrier coating may be applied at a weight selected from about 10 mg to about 60 mg/tablet and about 25 mg to about 50 mg/tablet. In general, a minimum weight is needed to ensure complete coverage of the tablet in light of imperfections in the tablet surface, and a maximum weight is determined by practical considerations, such as coating time, or by the need for better moisture protection.

As will be readily appreciated, the controlled release dosage form can be further provided with a cosmetic top coat. In one embodiment, a top-coat may be applied to an existing coating composition such as a moisture barrier. In certain embodiments, a cosmetic top-coat may include at least one of HPMC and copovidone. For example, when the controlled release dosage form includes a coated tablet comprising sodium oxybate as the drug, a top-coat including HPMC, such as for example an HPMC material selected from one or more of HPMC E3, E5, or E15, may be applied over a moisture barrier to improve the effectiveness of the moisture barrier by reducing any seepage of sodium oxybate and water from the surface of the coated tablet.

B. Immediate Release Formulations

The controlled release formulations described herein can be dosed together with an immediate release (IR) formulation. In one embodiment, the IR formulation may be provided as a separate formulation or dosage form that may be dosed together with a dosage form provided by a controlled release dosage form as described herein. The IR formulation may be provided in any suitable form, such as a dry powder formulation, a tablet or capsule unit dosage form, or a liquid formulation such as a solution or suspension formulation. As used herein, "immediate release" refers to a drug formulation that releases more than about 95% of the drug contained

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therein within a period of less than one hour after administration. In particular embodiments, the IR component of the compositions described herein release more than about 95% of the drug contained therein within a period selected from less than 45 minutes, less than 30 minutes, and less than 15 minutes post-administration. In other embodiments, the IR component of the compositions described herein release more than about 80% of the drug contained therein within a period selected from less than 45 minutes, less than 30 minutes, and less than 15 minutes post-administration.

In certain embodiments, the IR formulation is provided as an immediate release component of a controlled release dosage form as described herein. In one such embodiment, the IR component is provided as a coating over a controlled release component or formulation as described herein. A unit dosage form that integrates both controlled release and immediate release components can increase the convenience and accuracy with which a drug such as GHB is dosed to patients by providing a unit dosage form that not only provides quick onset of action, but also sustained delivery of GHB to the patient over a prolonged period of time. Furthermore, where the drug to be delivered is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, dosing controlled release and immediate release formulations together may avoid the disadvantages of the current GHB dosing regimens, which can result in highly pulsatile plasma concentrations.

I. Immediate Release Component

When the immediate release formulation is provided as an integrated IR component of a controlled release dosage form, the amount of drug included in the IR component may range from about 10% to 50% by weight of the total drug included in the integrated dosage form. As used herein, "integrated dosage form" refers to a single unit dosage form that includes both immediate release and controlled release components as described herein. For example, where the drug to be delivered from the immediate release and controlled release formulations incorporated into an integrated dosage form is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB in some embodiments, the drug included in the IR component may comprise about 10% to about 50% by weight of the total drug included in the unit dosage form. In one such embodiment, the drug included in the IR component of an integrated dosage form may comprise about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by weight of the total drug included in the unit dosage form. For example, an integrated dosage form as described herein may contain 1000 mg sodium oxybate, wherein 100 mg to 500 mg sodium oxybate (10% to 50% by weight) is contained within and delivered from the IR component and 500 mg to 900 mg sodium oxybate (50% to 90% by weight) is contained within and delivered from the CR component.

Where the IR component is provided as a coating over a controlled release dosage form, in certain embodiments, the drug included in the IR component may account for between about 75% and 98% by weight of the IR formulation. In the context of describing an IR component provided over a controlled release dosage form as described or disclosed herein, the controlled release dosage forms referred to include the controlled release formulations described herein, including, in specific embodiments, CR cores coated with a functional coating as described herein. Again, the drug included in such an embodiment may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. In certain embodiments,

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the IR component may comprise sodium oxybate in an amount of selected from a range of between about 75% and 98%, between about 80% and 98%, between about 85% and 98%, between about 90% and 98%, and between about 95% and 98% by weight.

An IR component formed as a coating over a controlled release dosage form as disclosed herein may be applied as a tableted overcoat according to conventional tablet coating and binding methods. Alternatively, an IR component formed as a coating over a controlled release dosage form as disclosed herein may be applied as a film coating, such as, for example, from a solution containing a suitable amount of drug and film former. In one such embodiment, wherein sodium oxybate is the drug included in the IR component, the coating forming the IR component may be coated over a controlled release dosage form from a coating solution that utilizes an alcohol and water solvent. For example, a suitable immediate release coating may be formed using a 20% solution of sodium oxybate in a 60%/40% (w/w) alcohol/water solution that contains a suitable film-former.

Where the IR component is provided as a film coat and includes one or more film-formers, suitable film formers may be selected from, for example, copovidone, hydroxypropyl cellulose, HPMC, and hydroxymethyl cellulose materials. An IR component containing sodium oxybate as the drug can be applied as a suspension or as a solution by adjusting the water content of the coating mixture. For a suspension, little or no water is added to the alcohol, and the example film formers should be suitable. To prepare a solution, however, the water content of the solvent is increased, for example to 40%, and a smaller set of film formers would be suitable due to the precipitation of most common film formers in the presence of sodium oxybate solution. Hypromellose is one of several potential film formers that is suitable. It is further possible, with more difficulty, to apply the sodium oxybate from an aqueous solution; however, the same limitations on film former applies, and processing is complicated by the hygroscopic nature of the drug. In one embodiment, the IR component useful for use in a controlled release dosage form as described herein includes 91% sodium oxybate and 9% hypromellose (HPMC E-15) that is applied from a solution containing 20% sodium oxybate and 2% HPMC E-15 in a 60/40 w/w ethanol/water solvent.

Where the IR component of an integrated dosage form is provided as a coating over the controlled release dosage form, the coating forming the IR component may further include one or more of an anti-tack agent and a plasticizer to facilitate processing and to improve film properties. Furthermore, addition of one or more surfactants, such as sodium lauryl sulfate, may improve the dissolution of IR coatings that contain hydrophobic components (such as anti-tack agents or water-insoluble film formers).

In embodiments where the IR component is provided as a coating over a controlled release formulation as described herein, the IR component may be positioned directly over the functional coating of the controlled release formulation. Where desired or necessary based on the drug to be delivered from the IR component and controlled release formulation included in such an integrated dosage form, the outer surface of the IR component may then be coated with a moisture barrier layer. For example, where the drug delivered by the integrated dosage form is highly hygroscopic, such as, for example, sodium oxybate, a moisture barrier layer over the immediate release coating forming the IR component may be provided.

The formulation and structure of integrated dosage forms as described herein can be adjusted to provide a combination of immediate release and controlled release performance that suits a particular dosing need. In particular, the formulation and structure of integrated dosage forms as described

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herein can be adjusted to provide any combination of the immediate release and controlled release performance characteristics described herein. In particular embodiments, for example, the drug delivered from an integrated dosage form as described herein is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, and the integrated dosage form sustains delivery of GHB over a period of from about 4 to about 10 hours. In one such embodiment, the IR component of the integrated dosage form provides rapid onset of action, releasing more than about 90% of the drug contained therein within a period of time selected from less than one hour, less than 45 minutes, less than 30 minutes and less than 15 minutes after administration, while the controlled release composition included in the integrated dosage form begins to deliver drug as the IR component is released and continues to deliver drug for a sustained period of between about 4 and about 10 hours. In another such embodiment, the IR component of the integrated dosage form provides rapid onset of action, releasing more than about 90% of the drug contained therein within a period of time selected from less than one hour, less than 45 minutes, less than 30 minutes and less than 15 minutes after administration, while the controlled release composition included in the integrated dosage form begins to deliver drug after the IR component is released and continues to deliver drug for a sustained period of between about 4 and about 10 hours.

Moreover, the ratio of drug release from the IR component and CR component can be adjusted as needed to facilitate a desired dosing regimen or achieve targeted dosing. A dosage form as described herein that integrates both IR and CR components may be formulated to deliver as much as 2,000 mg of a desired drug, such as GHB or a pharmaceutically acceptable salt, hydrate, tautomer, solvates or complex of GHB. In particular embodiments, the total amount of drug contained within an integrated IR/CR dosage form according to the present description may be between about 500 mg and about 1,400 mg. For example, in certain such embodiments, the total amount of drug may be selected from between about 500 mg and 1,400 mg, about 500 mg and 1,200 mg, about 500 mg and 1,100 mg, about 600 mg and 1,200 mg, about 600 mg and 1,100 mg, about 600 mg and 1,000 mg, about 600 mg and 950 mg, about 600 mg and 850 mg, about 600 mg and 750 mg, about 750 mg and 1,200 mg, about 750 mg and 1,100 mg, about 750 mg and 1,000 mg, about 750 mg and 950 mg, and about 750 mg and 850 mg. In an integrated IR/CR dosage form, the relative amounts of drug delivered from the IR component and CR components may be adjusted as desired as well. In particular embodiments, the ratio of drug released from the IR component to drug released from the CR component is from about 1:2 to about 1:4. In certain embodiments, such ratio is selected from about 1:2, 1:2.5, 1:3, 1:3.5 and 1:4.

In particular embodiments, the integrated dosage form may be formulated such that the controlled release formulation begins release of drug substantially simultaneously with delivery of the drug from the IR component. Alternatively, the integrated dosage form may be formulated such that controlled release formulation exhibits a start-up time lag. In one such embodiment, for example, the integrated dosage form may be formulated and configured such that start-up of delivery of drug from the controlled release composition occurs after delivery of drug from the IR component is substantially complete. Where a start-up lag time is desired, an enteric coating may be applied over the controlled release component (e.g., over a functional coating), but such a coating would necessarily limit the start-up lag to gastric residence and its associated variability. Use of enteric pore-formers would also impart a start-up lag, and such an embodiment would be more sensitive to food effects and gastric motility. Where a less pH-sensitive start-up lag time is desired, the delay may be accomplished or adjusted

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by the use of one or more coatings and films, including the functional coating provided over a CR core and, where utilized, the moisture barrier or cosmetic overcoats. In particular, start-up lag time as disclosed herein may be adjusted by modifying the formulation, thickness, and/or weight of the functional coating provided over the CR core, the moisture barrier layer or one or more non-functional or cosmetic overcoats.

EXAMPLES

Example 1—Controlled Release Core

A granulation used to form CR cores as described herein was manufactured in a 25 L high shear granulator according to the formula in Table 1A. Klucel EXF was divided into two equal portions; half of the Klucel EXF was dissolved in the ethanol, and half was dry blended with sodium oxybate. The material was initially granulated with 10% w/w ethanol and then titrated with another 3.5% w/w ethanol solution to achieve desired granule growth. A suitable wet mass was obtained at a total ethanol concentration of 13.5% w/w. The wet granules were divided into two sub lots and then each sub lot was dried in a 5-liter Niro fluid bed dryer. The dried granules were combined and milled through a COMIL equipped with a 14 mesh screen. Granulation parameters and particle size distribution are shown in Tables 1B and 1C, respectively.

The granulation was then combined with 2% magnesium stearate lubricant, and tablets were compressed on a 16-station press fitted with chrome-plated 0.325"×0.705" modified oval tooling. The average tablet hardness was 10.7 kiloponds.

TABLE 1A

Controlled Release Core Tablet Formulation			
Ingredient(s)		% w/w	mg/tablet
1	Sodium Oxybate	96.0	750.0
2	Hydroxypropyl cellulose, NF (Klucel EXF)	2.0	15.6
3	Ethanol, USP (200 proof)*	13.5	
4	Magnesium Stearate, NF	2.0	15.6
TOTAL		100.0	781.2

*Granulation solvent, removed during drying step

TABLE 1B

Granulation Parameters WET GRANULATION		
GRANULATION SOLUTION	250	
ADDITION RATE (G/MIN)		
TOTAL GRANULATION TIME (INCLUDING SOLUTION ADDITION AND WET MASSING TIME)	7 MINUTES	
IMPELLER SPEED (RPM)	300	
CHOPPER SPEED (RPM)	1800	
DRYING	SUBLOT 1	SUBLOT 2
DRYING INLET TEMPERATURE (° C.)	70	70
TOTAL DRYING TIME (MIN)	17	18
EXHAUST TEMPERATURE AT END OF DRYING (° C.)	47	48
LOD (% WT LOSS)	0.84	0.92

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TABLE 1C

Screen Analysis of Milled Granulation		
Screen size US Std mesh	Opening size microns	Wt Retained (%)
20	850	2.1
40	420	10.4
60	250	19.8
80	180	25.0
120	125	22.9
200	75	12.5
Pan	<45	7.3

Example 2—Functional Coating

Tablets from Example 1 were coated with a solution prepared according to the formulation in Table 2A. The ethylcellulose was first added to a 95/5 w/w mixture of ethanol and water and stirred until dissolved. Next, the hydroxypropyl cellulose and dibutyl sebacate were added and stirred until completely dissolved. 4.7 kg of tablets from Example 1 were then charged to an 8" pan Driam tablet coater and coated with the solution to 5.1 wt % gain (40 mg/tablet). The tablets were then dried for 5 minutes in the coater, and then finally cooled in the pan to an exhaust temperature below 30° C.

The dissolution profile was measured in de-ionized water using USP Apparatus 2 set to 37° C.±2° C. with paddles at 50 rpm. Samples were analyzed by HPLC. As shown in FIG. 1, the coated tablets exhibited controlled release with duration of approximately 6 hours. The dosage form released 12% of its contents after 1 hour, 34% after 2 hours, 71% after 4 hours, 93% after 6 hours, and 99% after 8 hours.

TABLE 2A

Formulation of Sodium Oxybate Sustained-Release Tablets			
Ingredient(s)		% of coat solids	% w/w of tablet
5	Sodium Oxybate tablet core		95.13
6	Hydroxypropyl cellulose, NF (Klucel EF)	37.0	1.80
7	Dibutyl sebacate	5.0	0.24
8	Ethylcellulose, NF (Ethocel Standard Premium 10)	58.0	2.82
9	Ethanol, USP (200 proof)*		
10	Purified water*		
TOTAL		100.0	100.00
			821.25

*Coating solvent, removed during processing

TABLE 2A

Coating Parameters for Driam 8" Pan Coater		
CR COATING	AVERAGE	RANGE
INLET TEMPERATURE (° C.)	46	42-55
EXHAUST TEMPERATURE (° C.)	43	41-46
INLET AIRFLOW (PASCAL)	>300	>300
ATOMIZATION PRESSURE (BAR)	2	2.0
SPRAY RATE (G/MIN)	35	32-37
PAN SPEED (RPM)	6	5-7

Example 3—Immediate-Release Overcoat

A solution of 20% sodium oxybate as active and 2.0% hypromellose E-15 (HPMC E-15) as film-former was pre-

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pared in 60/40 (w/w) ethanol/water. The coating solution was manufactured by first dissolving the HPMC E15 in water, then adding the ethanol and sodium oxybate. 3 kg of 750-mg strength sustained-release tablets from Example 2 were charged to a Driam tablet coater equipped with an 8" pan and preheated to 40° C. The entire coating solution was applied according to the parameters listed in Table 3A. The tablet weight gain was monitored every 5 minutes, and the coating was stopped when the entire solution was sprayed (the theoretical weight gain is 33.5%). The tablets were dried for 15 minutes; the tablets did not lose any weight during the 15 minute drying time, and so it was assumed that the drying was complete. The tablets were then cooled in the pan to an exhaust temperature of <30° C.

Analysis by HPLC revealed an overall potency of 961 mg, and thus a drug overcoat potency of 211 mg. Dissolution testing using USP Apparatus 2 set to 37° C.±2° C. with paddles at 50 rpm, shown in FIG. 2, demonstrates substantially the entire immediate-release overcoat is dissolved in 15 minutes and that controlled release is maintained for approximately 6 hours thereafter. Higher amounts of drug can be applied to the immediate release overcoat by using higher amounts of coating solution and extending the coating time accordingly.

TABLE 3A

Parameters for Immediate-Release Overcoating with 8" Driam Coater		
DRUG OVER-COATING	AVERAGE	RANGE
INLET TEMPERATURE (° C.)	59	55-63
EXHAUST TEMPERATURE (° C.)	51	50-53
PRODUCT TEMPERATURE (° C.)	43	41-49
INLET AIRFLOW (PASCAL)	>300	>300
ATOMIZATION PRESSURE (BAR)	2	2
SPRAY RATE (G/MIN)	16	14-17
PAN SPEED (RPM)	8	7-8
TOTAL RUN TIME (HRS)	4 HRS 47 MIN (COATING) 15 MIN (DRYING)	

The following examples illustrate aspects of the sustained-release coating formulation with several evaluations using tablets from Example 1.

Example 4—Effect of Membrane Weight with Poloxamer as Pore Former in Functional Coating

One means of controlling dissolution is by adjustment of the coating thickness, or amount of film applied to each tablet. This was illustrated with a film consisting of 33% poloxamer 188 (P188) and 67% ethylcellulose 10 cPs (EC-10). The coating solution was prepared by dissolving 3.59 grams of EC-10 and 1.77 grams of P188 in a mixture of 80 grams denatured alcohol ("alcohol") and 4 grams de-ionized water. (Denatured alcohol, S-L-X manufactured by W. M. Barr, is approximately a 50/50 w/w blend of methanol and ethanol.)

Twelve tablets from Example 1 were coated in a Caleva Mini-coater/Drier 2 under parameters listed in Table 4A. Periodically, the tablets were removed and weighed to determine film weight. Three tablets were removed at times corresponding to 21 mg, 30 mg, 40 mg, and finally 60 mg weight gain.

The dissolution profiles were measured with USP Apparatus 7 (Vankel Bio-dis) set to 37° C.±2° C. and using a dipping rate of 30/minute, tablets fixed in plastic holders and intervals corresponding to 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, and 14 h (each interval is 50 ml volume). The tubes were analyzed by conductivity, and results are calculated as percent of total amount. The results demonstrate that controlled release is achieved with membrane weights rang-

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ing from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

TABLE 4A

Standard Parameters for Sustained-Release Coating in Caleva Mini-Coater/Drier 2	
Parameter	Setting
Batch size	3-12 Tablets
Inlet temperature	40° C.
Air flow setting	70-85%
Solution flow rate	18 ml/hr
Agitator setting	32
Atomization pressure	0.5 bar
Gun position	Adjusted to achieve desired deposition

Example 5—Effect of Membrane Weight with Hydroxypropyl Cellulose as Pore Former in Functional Coating

Following procedures of Example 4, 12 tablets from Example 1 were coated with a film consisting of 36.5% HPC-EF, 5.0% dibutyl sebacate (DBS), and 58.5% EC-10 (all percentages by weight) coated from a solution consisting of 7% solids in 95/5 alcohol/water. The results shown in FIG. 4 demonstrate that controlled release over a relevant time period is achieved with membrane weights ranging from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

Example 6—Effect of Poloxamer Level in Functional Coating

In addition to adjustment of membrane weight, another useful means of controlling release rate or duration is by adjustment of the pore-former content of the formulation. Following procedures of Example 4, two additional solutions consisting of (a) 25% P188 by weight/75% EC-10 by weight and (b) 40% P188 by weight/60% EC-10 by weight were prepared as 7% (w/w) solutions in 95/5 alcohol/water. In each of the two separate coatings, four tablets from Example 1 were coated to 41 mg. The dissolution profiles are shown in FIG. 5, along with that of the 40 mg set of Example 4 for comparison. The results demonstrate that poloxamer level can be adjusted at least over the range of 25%-40% by weight, while still providing controlled release of the drug.

Example 7—Effect of Hydroxypropyl Cellulose Level in Functional Coating

In a fashion similar to Example 6, the effect of HPC level in the functional coating was evaluated over the range of 30%-50% by weight. Three separate coating solutions were prepared with 30%, 40%, and 50% HPC-EF; 5% DBS; and the balance EC-10. All solutions were prepared with 7% total components in 95/5 alcohol/water. In each coating, 4 tablets from Example 1 were coated to 40-41 mg/tablet weight gain. The dissolution profiles shown in FIG. 6 demonstrate controlled release of the drug was achieved with HPC levels of at least 30-50% by weight.

Example 8—Effect of Hydroxypropyl Cellulose Molecular Weight when used in Functional Coating

Hydroxypropyl cellulose is supplied in several molecular weight grades, many of which may be suitable for use as pore-formers in ethylcellulose films. Two such grades (Klu-

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cel "EF" and "JF", supplied by Ashland) corresponding to 80,000 daltons and 140,000 daltons were evaluated with other components fixed. Following procedures of Example 4, solutions were prepared with 40% HPC, 5% DBS, and 55% EC-10 (all percentages by weight) using 7% total components in 95/5 alcohol/water. In each coating, 4 tablets from Example 1 were coated to 40-41 mg/tablet weight gain. The results shown in FIG. 7 demonstrate a modest effect of molecular weight and that the two grades tested provide for acceptable release profiles.

Example 9—Effect of Ethylcellulose Molecular Weight or Viscosity

Another consideration is the molecular weight, or viscosity, of ethylcellulose. Two grades were evaluated, corresponding to 4 cPs and 10 cPs viscosity for a 5% solution. Following procedures of Example 4, two solutions were prepared corresponding to 58.5 wt % ethylcellulose (EC-4 or EC-10), 36.5 wt % HPC-EF, and 5.0 wt % DBS having 7% w/w total components in 95/5 alcohol/water. Tablets from Example 1 were coated to 40 mg/tablet weight gain, and dissolution profiles are shown as FIG. 8. The results indicate both grades of ethylcellulose provide for acceptable profiles, and suggest that other ethylcellulose grades (such as 20 cPs) may also be acceptable.

Example 10—Demonstration of Alcohol Ruggedness of Controlled Release Sodium Oxybate Tablets

Co-administration of sustained-release dosage forms with alcoholic beverages is a relevant concern, as ethanol is known to dissolve certain rate-controlling components that would not otherwise be dissolved. In some dosage forms, this may lead to dose-dumping. As ethanol is rapidly absorbed in the stomach, a relevant test involves dissolution of the dosage form in vodka (40% ethanol nominal) for 2 hours (representing gastric retention time), followed by normal dissolution in de-ionized water.

This test was performed on sustained-release tablets from Example 9 (36.5 wt % HPC EF, 5 wt % DBS, 58.5 wt % EC-4). The analysis of sodium oxybate by conductivity was corrected for the different response in vodka vs. de-ionized water. The results shown in FIG. 9A indicate that dissolution is slower in Vodka, and that no dose-dumping occurred.

Likewise, a similar test was performed on sustained-release tablets with a film comprised of 33 wt % P188 and 67 wt % EC-10. Those results, shown in FIG. 9B, also indicate slower release in vodka and no dose-dumping.

Example 11—Aqueous Coating of Controlled Release Film

Due to the hygroscopic nature of sodium oxybate, coating the rate-controlling film from an alcoholic solution is desirable. However, use of ethylcellulose aqueous dispersions is attractive for environmental and cost considerations. A film consisting of 30 wt % HPC EF and 70 wt % Surelease (aqueous ethylcellulose dispersion) was deposited on tablets from Example 1 as follows. First, 1.37 grams of HPC EF was dissolved in 22.6 grams de-ionized water. This was then poured into 32.5 grams of Surelease E-7-19040-clear while stirring. Eight tablets were coated in the Caleva Mini-coater/Drier 2 with flow rate of 15 ml/hr and 58° C. inlet temperature. Samples removed at 24 mg and 40 mg were then tested for dissolution, with no post-coating heat treatment. The results are shown in FIG. 10.

Example 12—Calcium Oxybate Controlled Release

A controlled release dosage form for delivery of calcium oxybate was prepared by generally following procedures of

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Example 1 found in U.S. Pat. No. 4,393,296 (Klosa, Production of Nonhygroscopic Salts of 4-Hydroxybutyric Acid). The isolated calcium oxybate was milled to pass through a 16-mesh screen. For this study, a small sample comprising 9.3 grams of calcium oxybate was blended with 0.19 grams of sodium stearyl fumarate (Pruv, JRS Pharma, Rosenberg, Germany). 800 mg aliquots of this 98% calcium oxybate and 2% sodium stearyl fumarate were then directly compressed into tablets using 0.325"x0.705" modified oval tooling and a Carver press with 1-ton applied force. Following procedures of Example 4, nine tablets were coated with a film having 33% poloxamer 188 and 67% EC-10 from a solution of 7% w/w solids in 95/5 alcohol/water. Two tablets were removed at each intermediate coating weight corresponding to 20 mg, 32 mg, 41 mg, and finally at 60 mg. The dissolution profiles are shown as FIG. 11. These results using calcium oxybate follow the general behavior of sodium oxybate demonstrated in Example 4.

Example 13—Clinical Evaluation of Controlled Release Dosage Forms

An open-ended, randomized, crossover study was conducted to evaluate controlled release dosage forms as described herein. The controlled release dosage forms were formulated to deliver sodium oxybate and were compared to a sodium oxybate oral solution (commercially available as Xyrem® (sodium oxybate) oral solution). The study was conducted in healthy male and female volunteers.

Four different sodium oxybate formulations were administered to patients. The first, designated herein as Treatment A, was the sodium oxybate oral solution containing 375 mg/ml sodium oxybate. Treatments B through E, as designated herein, involved administration of three controlled release dosage forms (Treatments B through D), with one of the controlled release dosage forms being used to administer two different doses of sodium oxybate (Treatments D and E). The controlled release dosage forms administered as Treatment B included 750 mg sodium oxybate per dosage form and were produced with a CR core and functional overcoat as described in Example 1 and Example 2, the controlled release dosage forms administered as Treatment C included 750 mg sodium oxybate per dosage form and were produced as described in Example 1 and Example 4, and the controlled release dosage forms administered as Treatments D and E included 1,000 mg sodium oxybate per dosage form and were produced with a CR core (750 mg sodium oxybate), functional overcoat, and IR overcoat (250 mg sodium oxybate) as described in Examples 1 through 3.

Patients were divided into two groups. The first group received Treatment A, Treatment B, and Treatment C over the course of the clinical study, with a washout period between each treatment. Treatment A was administered to each patient as two 3 g doses given four hours apart (one dose at time zero and the second dose four hours later), for a total dose of 6 g sodium oxybate. Treatments B and C were administered to each patient only at time zero, with each treatment being administered as 8 tablets, providing a total dose of 6 g sodium oxybate. Blood samples from each patient were taken at various intervals and analyzed by LC/MS for total sodium oxybate content in the plasma. A total of 29 patients received Treatment A, a total of 19 patients received Treatment B, and a total of 19 patients received Treatment C. The mean plasma concentration of sodium oxybate over time achieved by each of the treatments is shown in FIG. 12 (Treatment A and Treatment B) and FIG. 13 (Treatment A and Treatment C), and a summary of pharmacokinetic parameters provided by Treatments A through C are provided in Table 5.

TABLE 5

Summary of PK Parameters for Treatments A, B, C						
	λ_{z} (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) ^a	Cmax (ug/ml)	AUClast (hr * ug/ml)	AUCinf (hr * ug/ml)
Treatment A						
N	29	29	29	29	29	29
Mean	1.22	0.60	4.50 (0.5, 4.75)	130.79	350.84	351.20
SD	0.27	0.13		31.52	116.74	116.74
CV %	21.93	22.61		24.10	33.27	33.24
Mean	1.19	0.58		127.37	333.33	333.72
Treatment B						
N	18	18	19	19	19	18
Mean	0.62	1.22	2.00 (1.50, 5.00)	41.78	188.23	196.25
SD	0.16	0.40		18.40	103.60	102.50
CV %	26.44	32.58		44.03	55.04	52.23
Mean	0.59	1.17		38.46	163.80	173.33
Treatment C						
N	19	19	19	19	19	19
Mean	0.74	0.99	2.50 (1.00, 5.00)	50.49	221.64	222.60
SD	0.16	0.23		15.83	106.85	106.80
CV %	22.25	22.93		31.35	48.21	47.98
Mean	0.72	0.96		48.10	200.08	201.12

The second group was administered Treatment A, Treatment D, and Treatment E during over the course of the clinical study, with a washout period between each treatment. Again, Treatment A was administered to each patient as two 3 g doses given four hours apart (one dose at time

a total of 30 patients received Treatments D and E. The mean plasma concentration of sodium oxybate over time achieved by each of the treatments is shown in FIG. 14, and a summary of pharmacokinetic parameters provided by Treatments A through C are provided in Table 6.

TABLE 6

Summary of PK Parameters for Treatments A, D, E						
	λ_{z} (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) ^a	Cmax (ug/ml)	AUClast (hr * ug/ml)	AUCinf (hr * ug/ml)
Treatment A						
N	30	30	30	30	30	30
Mean	1.08	0.71	4.50 (0.50, 5.50)	114.59	301.28	301.59
SD	0.31	0.27		27.91	100.85	100.87
CV %	29.00	37.90		24.36	33.47	33.45
Mean	1.03	0.67		111.20	285.47	285.79
Treatment D						
N	30	30	30	30	30	30
Mean	0.46	1.63	0.75 (0.50, 2.50)	25.10	64.44	65.58
SD	0.14	0.47		7.33	20.36	20.26
CV %	30.27	29.00		29.20	31.60	30.90
Mean	0.44	1.56		24.01	61.31	62.55
Treatment E						
N	30	30	30	30	30	30
Mean	0.59	1.36	1.00 (0.50, 5.00)	59.52	242.30	243.80
SD	0.20	0.64		17.72	117.15	116.79
CV %	34.57	46.91		29.77	48.35	47.91
Mean	0.55	1.25		56.89	216.33	218.12

^a Tmax is summarized as median (min, max).

zero and the second dose four hours later), for a total dose of 6 g sodium oxybate. Treatments D and E were administered to each patient only at time zero. Patients receiving Treatment D were administered 4 tablets at time zero, providing a total dose of 4 g sodium oxybate, and patients receiving Treatment E were administered 8 tablets at time zero, providing a total dose of 8 g sodium oxybate. Blood samples from each patient were taken at various intervals and analyzed by LC/MS for total sodium oxybate content in the plasma. A total of 30 patients received Treatment A, and

It will be obvious to those having skill in the art that many changes may be made to the details of the above-described embodiments without departing from the underlying principles of the invention. The scope of the present invention should, therefore, be determined only by the following claims.

The invention claimed is:
1. A method for treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof comprising delivering to the patient a formulation

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comprising immediate release and sustained release portions, each portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, wherein:

- a. the sustained release portion comprises a functional coating and a core, wherein the functional coating is deposited over the core, wherein the core comprises at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; the sustained release portion comprises about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm;
 - b. the immediate release portion comprises about 75% and about 98% by weight of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, and the amount of gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the immediate release portion is about 10% to 50% by weight of the total gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the formulation;
 - c. the formulation releases at least about 30% of its gamma-hydroxybutyrate by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm; and
 - d. the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.
2. The method of claim 1 wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 7 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.
3. The method of claim 1 wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.
4. The method of claim 1 wherein the sustained release portion releases about 60% to about 90% of its gamma-hydroxybutyrate by about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.
5. The method of claim 1 wherein the sustained release portion comprises hydrogenated vegetable oil, hydrogenated castor oil, or mixtures thereof.
6. The method of claim 1 wherein the formulation comprises a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.
7. The method of claim 6 wherein the formulation comprises a sodium salt of gamma-hydroxybutyrate.

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8. The method of claim 1 wherein the immediate release portion comprises 50% by weight of the total gamma-hydroxybutyrate.

9. The method of claim 1, wherein the one or more methacrylic acid-methyl methacrylate co-polymers comprise from about 30% to about 45% by weight of the functional coating.

10. The method of claim 1 wherein the sustained release portion releases about 10% or less of its gamma-hydroxybutyrate by about 1 hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

11. A method for treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof comprising delivering to the patient a formulation of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, comprising immediate release and a solid sustained release portions:

- a. wherein the immediate release portion comprises about 55 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate;
- b. wherein the sustained release portion comprises from about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate and a functional coating deposited over a core comprising the at least one pharmaceutically active ingredient, wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm;
- c. the formulation releases at least about 30% of its gamma-hydroxybutyrate or salt thereof by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm; and
- d. the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

12. A method for treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof comprising delivering to the patient a formulation comprising immediate release and sustained release portions, each portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, wherein:

- a. the sustained release portion comprises a functional coating and a core, wherein the functional coating is deposited over the core, wherein the core comprises at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate; wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; the sustained release portion comprises about 500 mg to 12 g of at least one pharmaceutically

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- active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm;
- b. the immediate release portion further comprises one or more pharmaceutically acceptable excipients selected from the group consisting of copovidone, plasacryl, hydroxypropyl cellulose, hydroxypropyl methylcellulose and hydroxymethyl cellulose, and the amount of gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the immediate release portion is about 10% to 50% by weight of total gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the formulation;
- c. the formulation releases at least about 30% of its gamma-hydroxybutyrate by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm; and
- d. the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.
13. The method of claim 12, wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 7 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.
14. The method of claim 12, wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.
15. The method of claim 12, wherein the sustained release portion releases about 60% to about 90% of its gamma-hydroxybutyrate by about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.
16. The method of claim 12, wherein the sustained release portion comprises hydrogenated vegetable oil, hydrogenated castor oil, or mixtures thereof.
17. The method of claim 12, wherein the formulation comprises a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.
18. The method of claim 17, wherein the formulation comprises a sodium salt of gamma-hydroxybutyrate.
19. The method of claim 12, wherein the immediate release portion comprises 50% by weight of the total gamma-hydroxybutyrate.
20. The method of claim 12, wherein the one or more methacrylic acid-methyl methacrylate co-polymers comprise from about 30% to about 45% by weight of the functional coating.
21. The method of claim 12, wherein the one or more pharmaceutically acceptable excipients comprise hydroxypropyl cellulose.

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22. The method of claim 12, wherein the one or more pharmaceutically acceptable excipients comprise hydroxypropyl methylcellulose.
23. The method of claim 12, wherein the one or more pharmaceutically acceptable excipients are about 10% by weight of the immediate release portion.
24. The method of claim 12, wherein the sustained release portion releases about 10% or less of its gamma-hydroxybutyrate by about 1 hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.
25. A method for treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof comprising delivering to the patient a formulation of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, comprising immediate release and a solid sustained release portions:
- a. wherein the immediate release portion comprises about 55 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate and about 10% by weight of one or more pharmaceutically acceptable excipients selected from the group consisting of copovidone, plasacryl, hydroxypropyl cellulose, hydroxypropyl methylcellulose and hydroxymethyl cellulose;
- b. wherein the sustained release portion comprises from about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate and a functional coating deposited over a core comprising the at least one pharmaceutically active ingredient, wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm;
- c. the formulation releases at least about 30% of its gamma-hydroxybutyrate or salt thereof by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm; and
- d. the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.
26. The method of claim 25, wherein the one or more pharmaceutically acceptable excipients comprise hydroxypropyl methylcellulose.
27. The method of claim 25, wherein the one or more pharmaceutically acceptable excipients comprise hydroxypropyl cellulose.

* * * * *

EXHIBIT 2



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(12) **United States Patent**
Allphin et al.

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(54) **CONTROLLED RELEASE DOSAGE FORMS
FOR HIGH DOSE, WATER SOLUBLE AND
HYGROSCOPIC DRUG SUBSTANCES**

(71) Applicant: **JAZZ PHARMACEUTICALS, INC.**,
Palo Alto, CA (US)

(72) Inventors: **Clark Allphin**, Seattle, WA (US);
James Pfeiffer, Palo Alto, CA (US)

(73) Assignee: **JAZZ PHARMACEUTICALS, INC.**,
Palo Alto, CA (US)

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No. 16/025,487, filed on Jul. 2, 2018, now Pat. No.
10,758,488, which is a continuation of application
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(58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — Patricia Duffy

Assistant Examiner — Garen Gotfredson

(74) *Attorney, Agent, or Firm* — Cooley LLP

(57) **ABSTRACT**

Controlled release dosage forms are described herein. The controlled release formulations described herein provide prolonged delivery of high dose drugs that are highly water soluble and highly hygroscopic. In specific embodiments, controlled release dosage forms for delivery of a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. The controlled release dosage forms described herein may incorporate both controlled release and immediate release formulations in a single unit dosage form.

15 Claims, 9 Drawing Sheets

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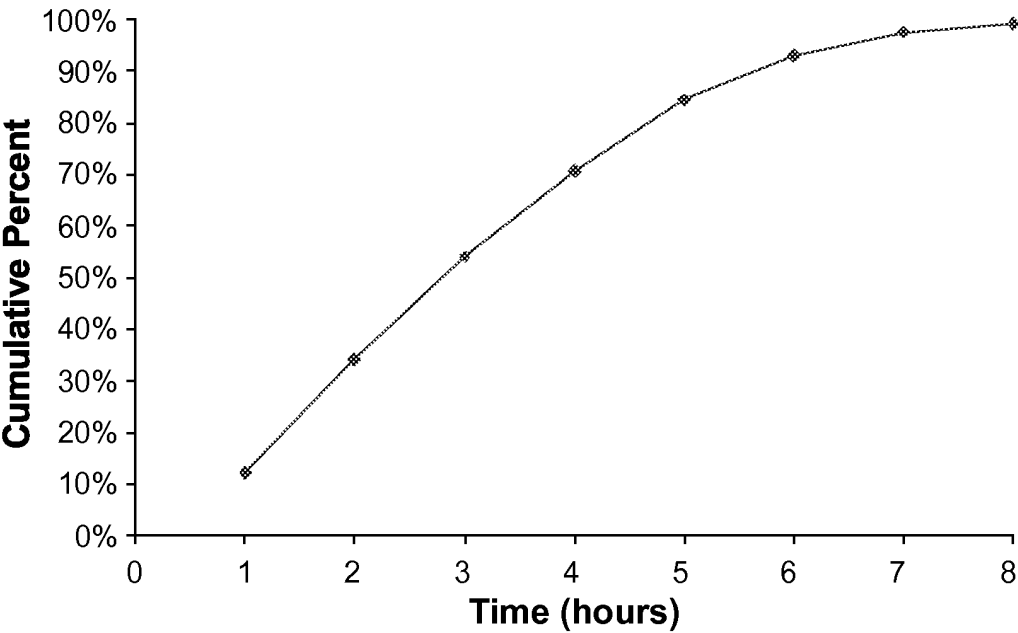


FIG. 1

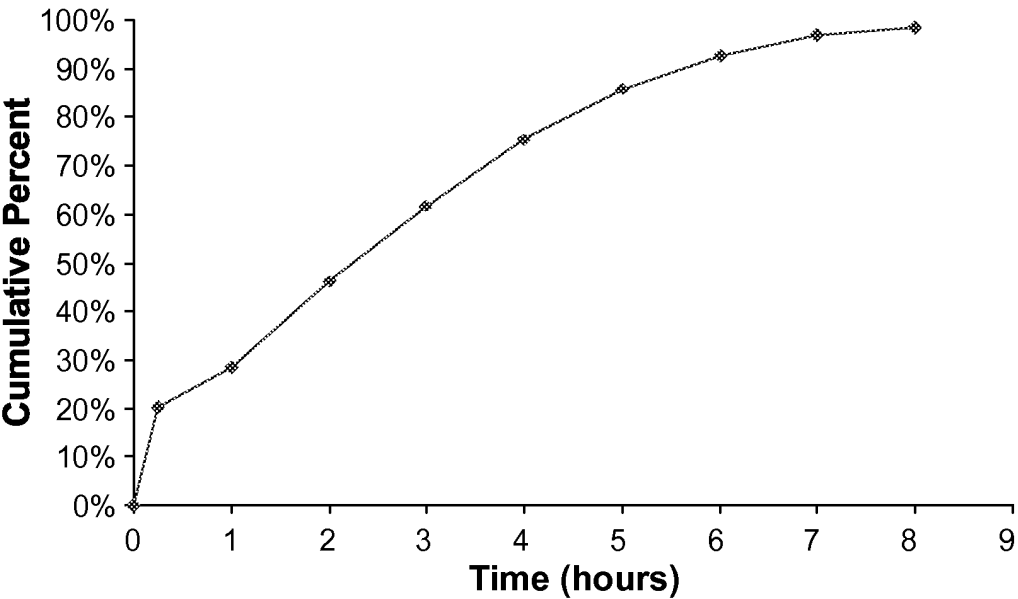


FIG. 2

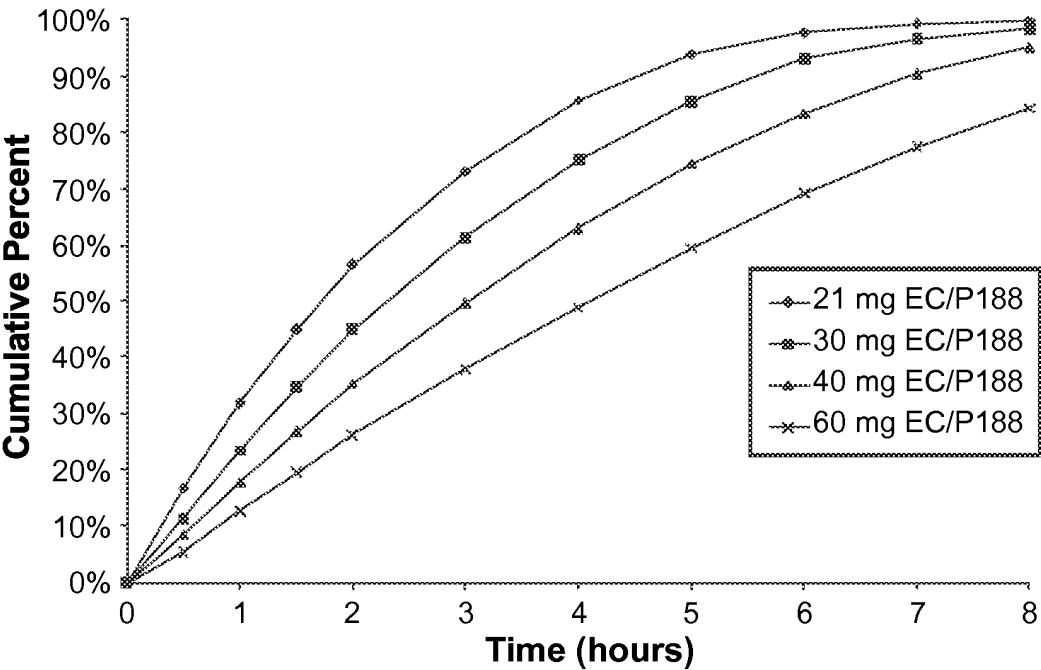


FIG. 3

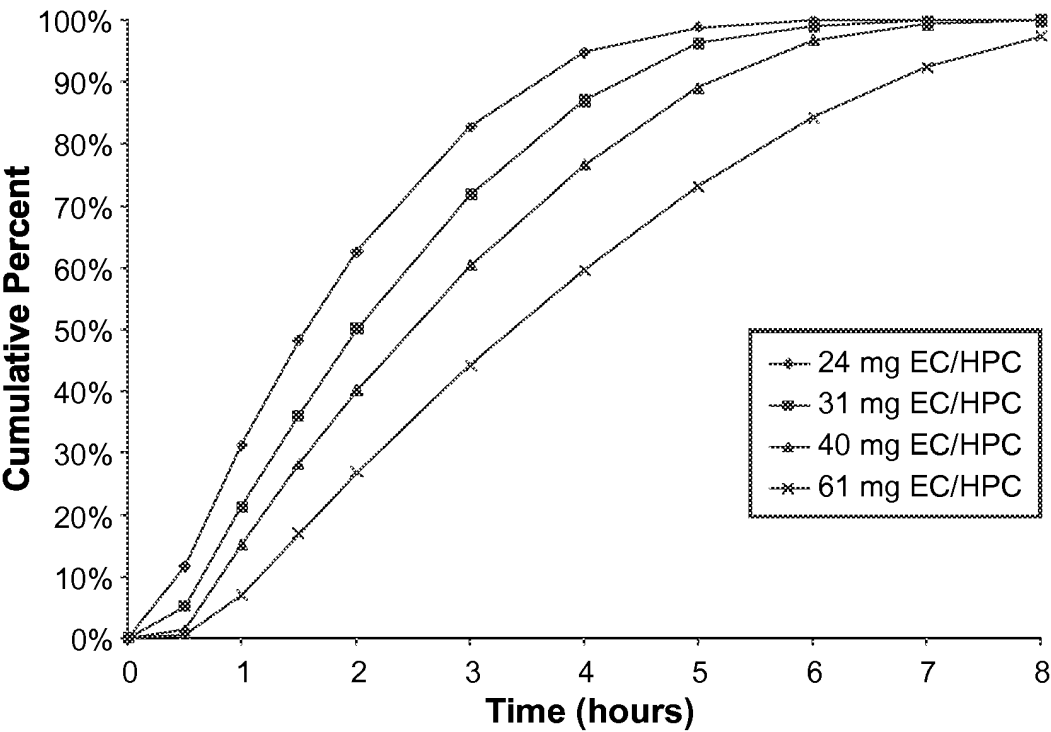


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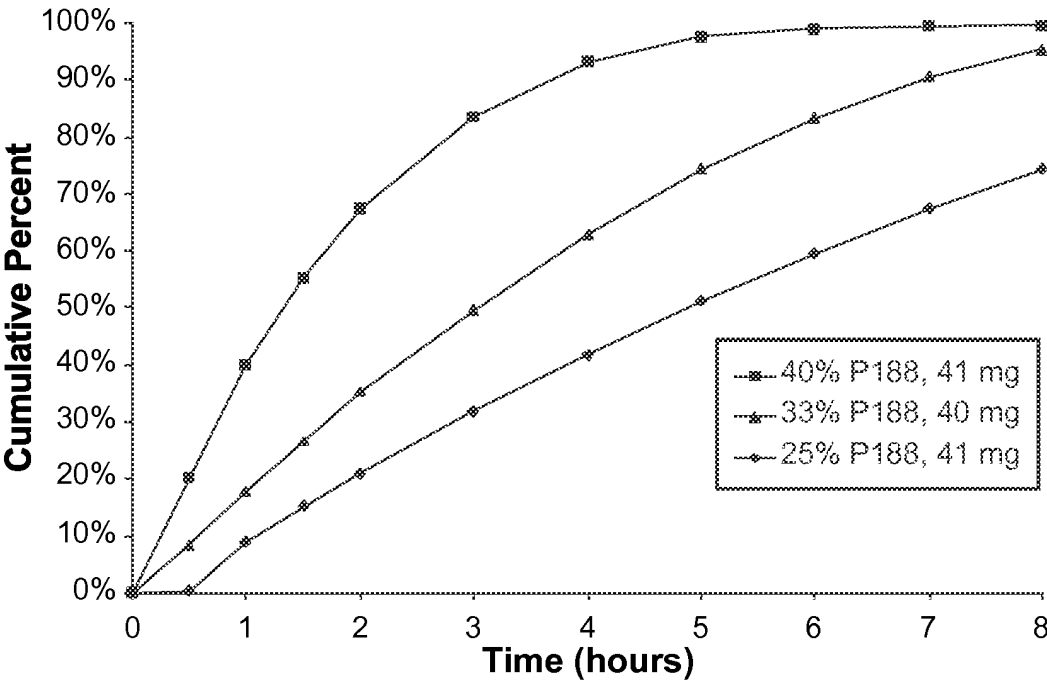


FIG. 5

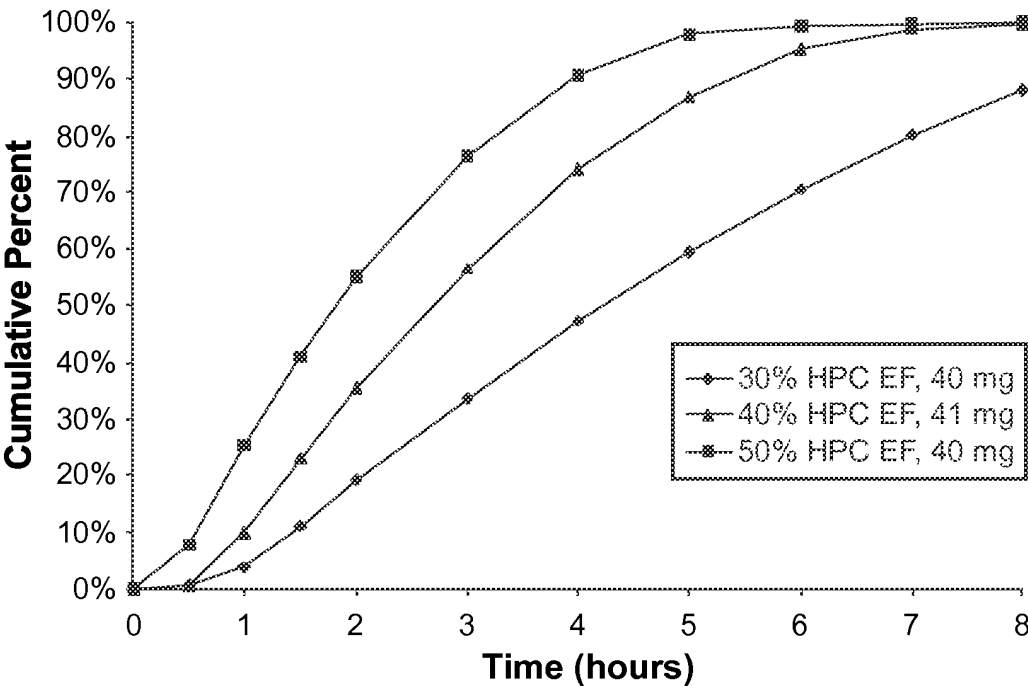


FIG. 6

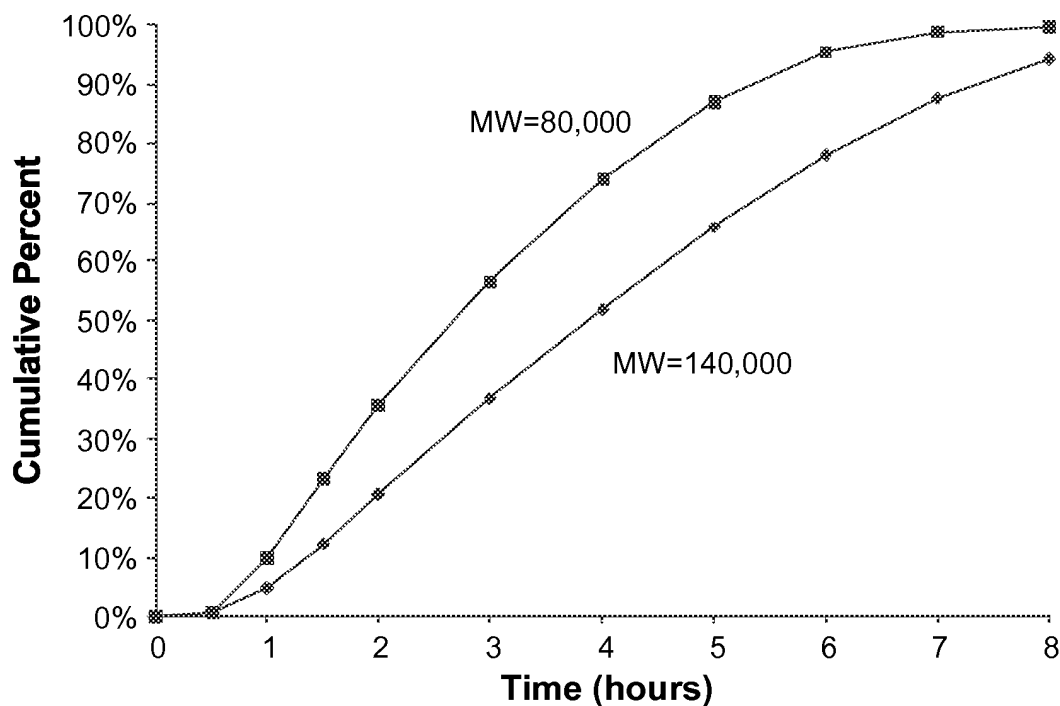


FIG. 7

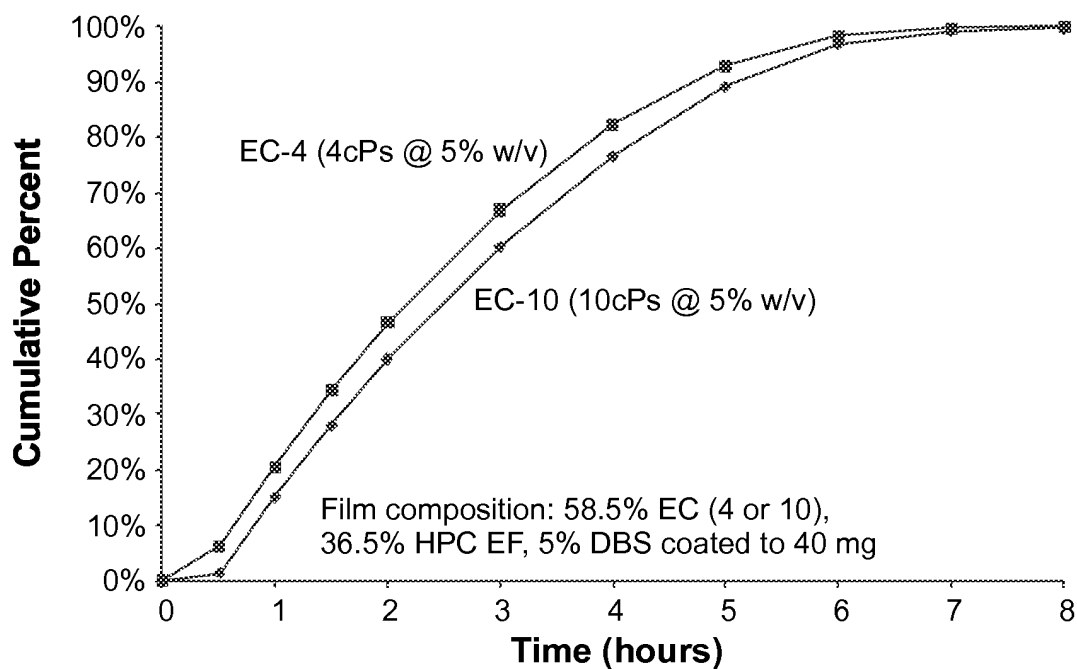


FIG. 8

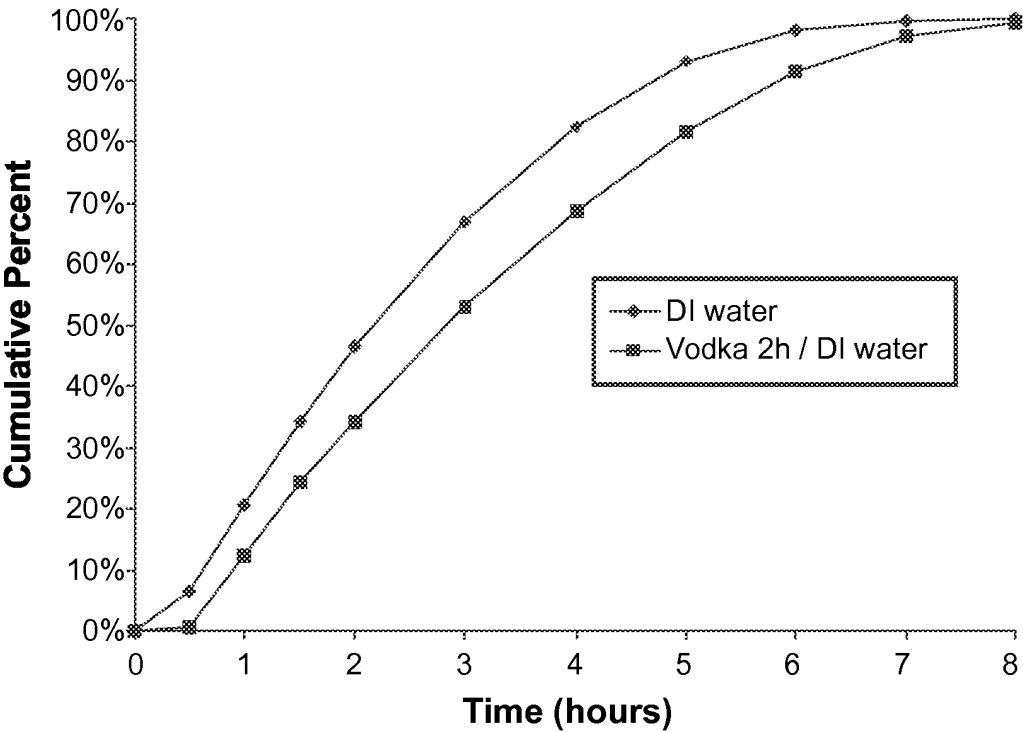


FIG. 9A

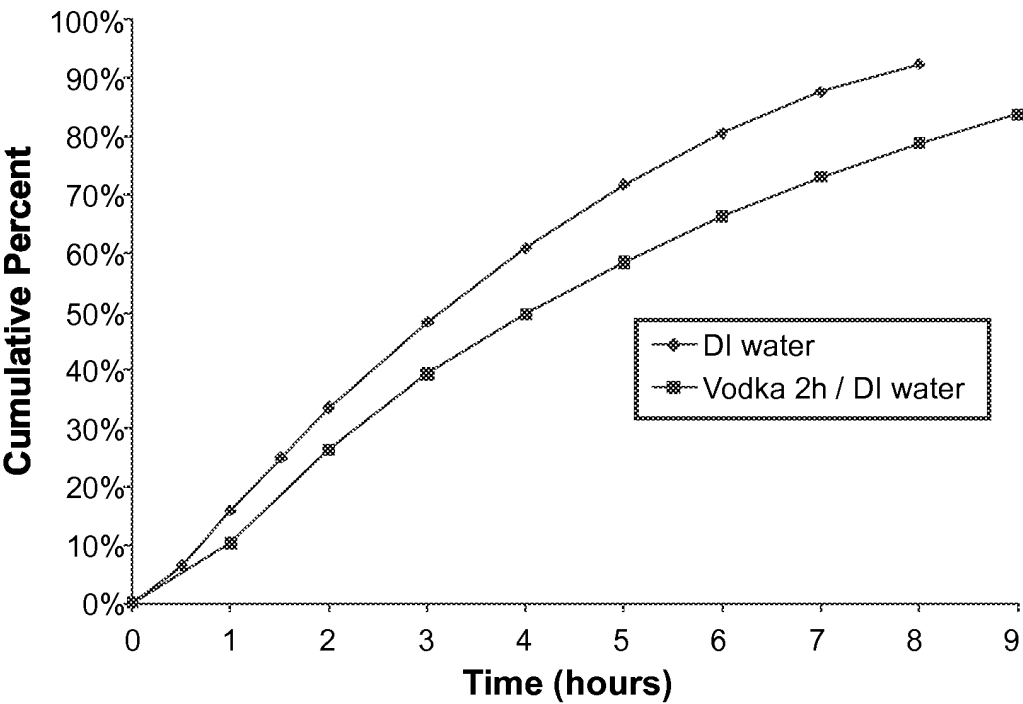


FIG. 9B

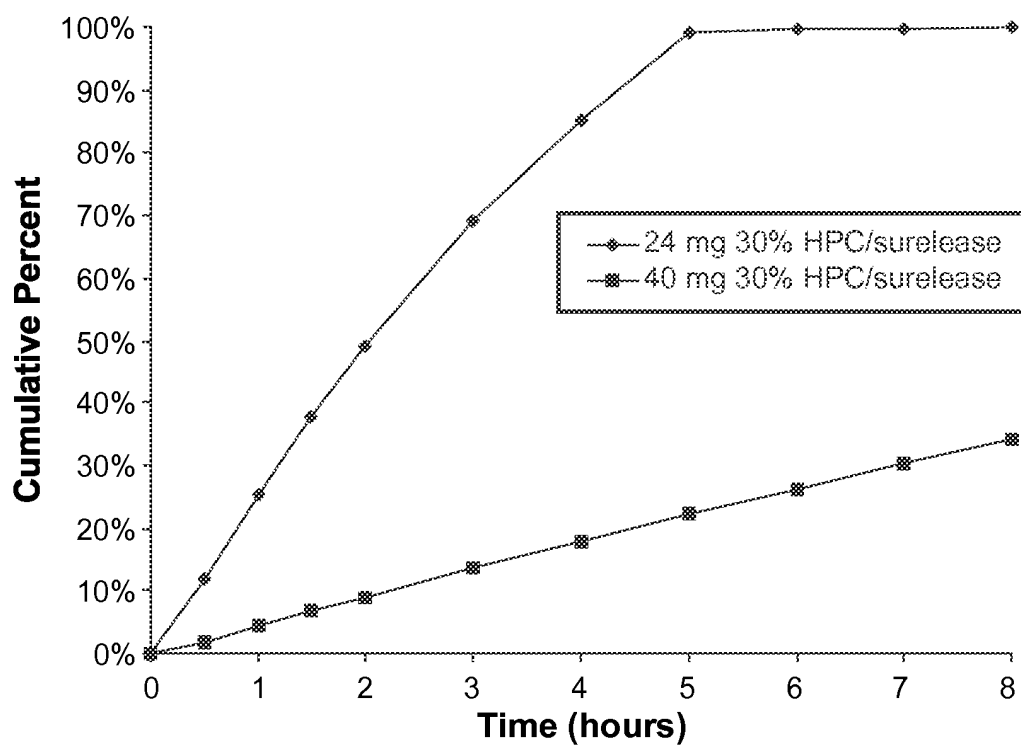


FIG. 10

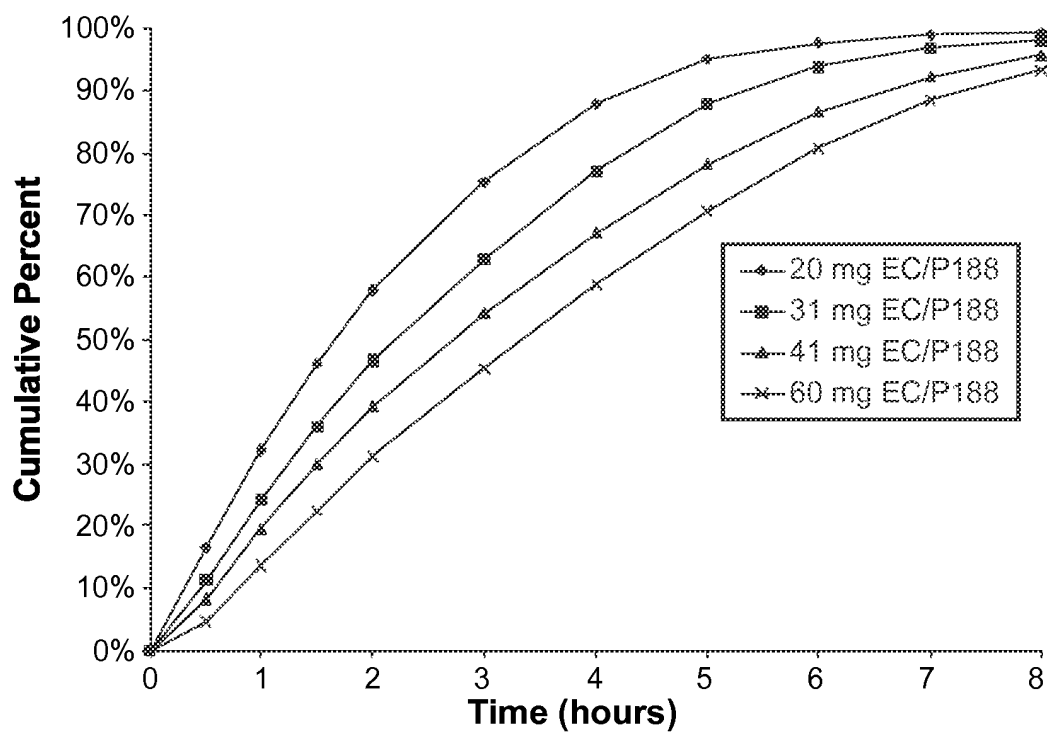


FIG. 11

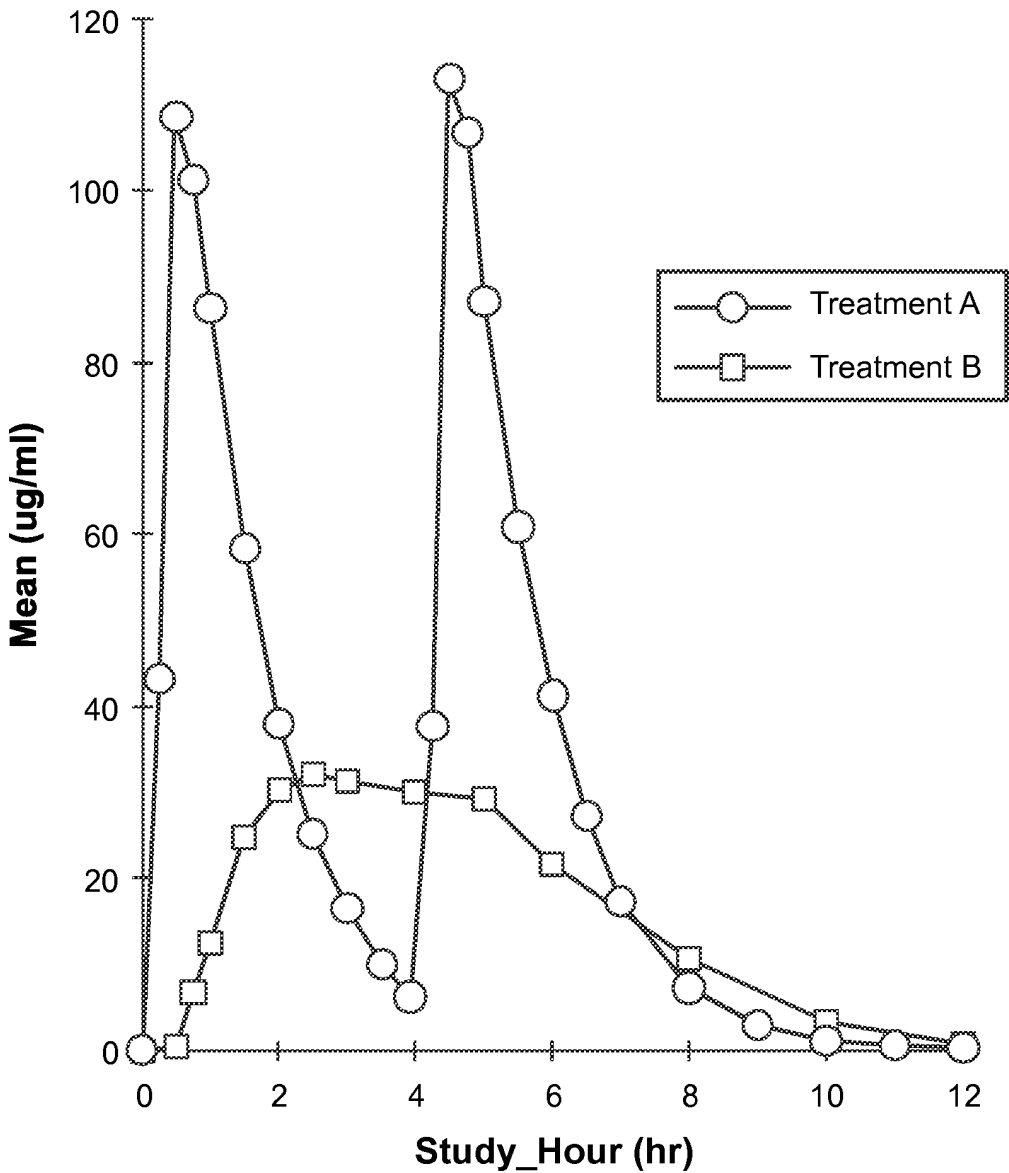


FIG. 12

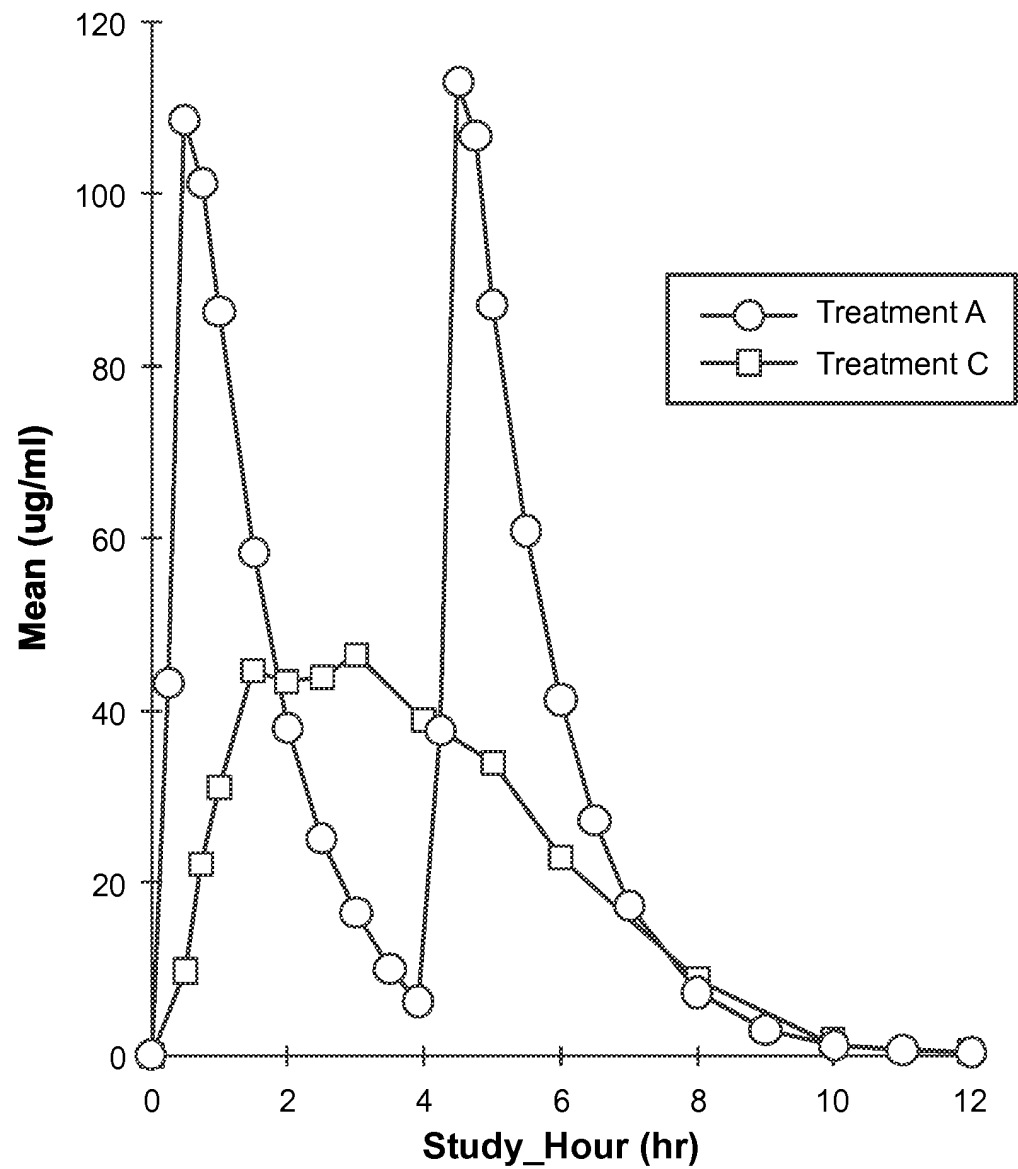


FIG. 13

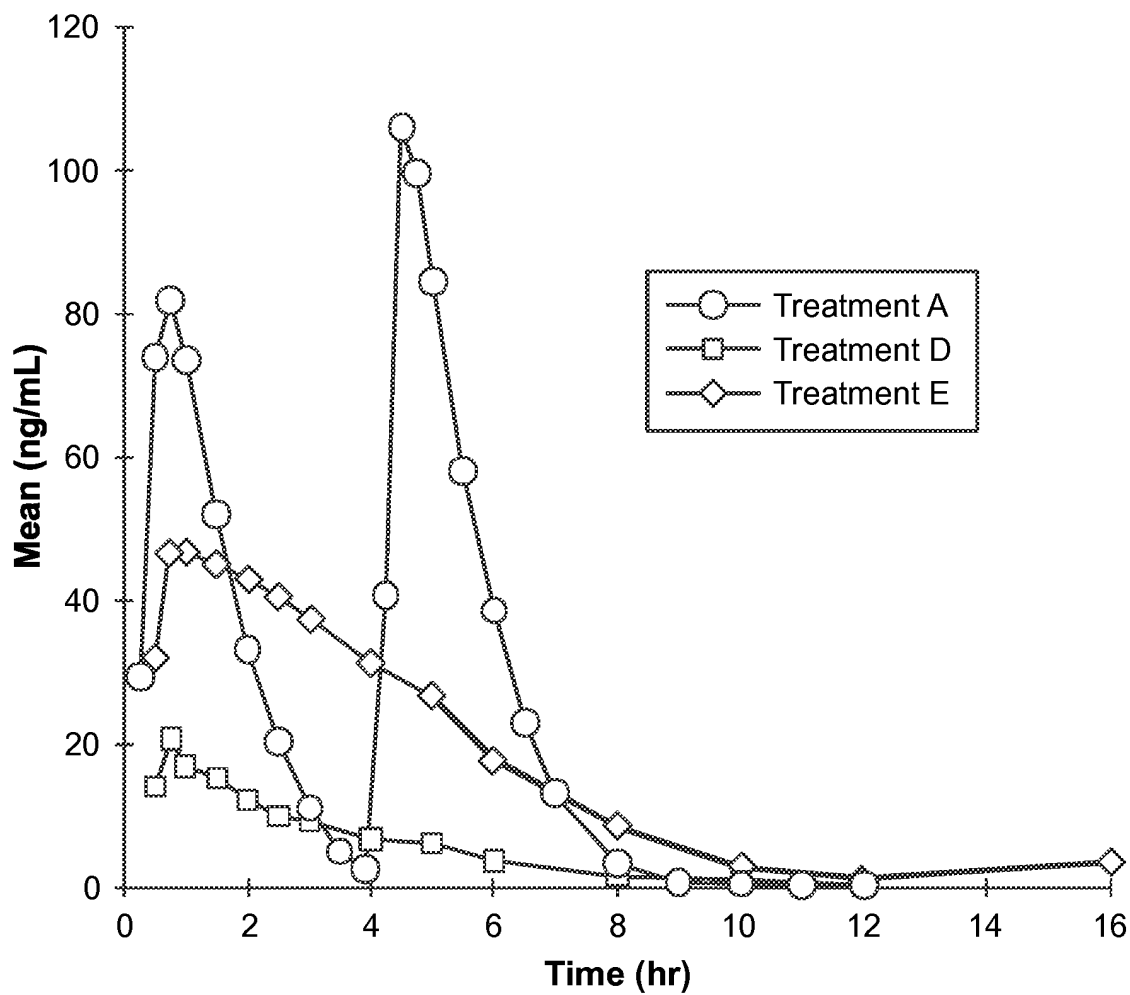


FIG. 14

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CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 16/916,677, filed Jun. 30, 2020, which is a continuation of U.S. patent application Ser. No. 16/712,260, filed Dec. 12, 2019, which is a continuation of U.S. patent application Ser. No. 16/025,487, filed Jul. 2, 2018, now U.S. Pat. No. 10,758,488, which is a continuation of U.S. patent application Ser. No. 13/071,369, filed Mar. 24, 2011, now abandoned, which claims the benefit of U.S. Provisional Application No. 61/317,212, filed on Mar. 24, 2010, the contents of each of which are incorporated herein by reference.

TECHNICAL FIELD

This disclosure relates to controlled release drug compositions.

BACKGROUND

For some drugs, it is difficult to formulate a controlled release dosage form that maintains an effective concentration of the drug over a sustained period of time. In particular, drugs that are administered at a high dose, drugs having a low molecular weight, and drugs with high water solubility make formulation of a controlled release dosage form challenging. For example, in the context of a controlled release drug formulation produced as a unit dosage form for oral administration, drugs that must be administered at a high dose constrain the amount of rate controlling excipients that can be used in formulating a drug composition that is both capable of sustained delivery of therapeutic doses of the drug and exhibits a size and shape suited to oral administration. Low molecular weight and high-solubility drugs may also readily permeate films and matrices that might otherwise be used to control release, and high solubility drugs are not suited to some drug delivery approaches, particularly where zero-order release kinetics are desired. An example of a drug that is administered at a high dose, has a low molecular weight, and high water solubility, is gamma-hydroxy butyrate (GHB), particularly the sodium salt of GHB.

Initial interest in the use of GHB as a potential treatment for narcolepsy arose from observations made during the use of GHB for anesthesia. Unlike traditional hypnotics, GHB induces sleep that closely resembles normal, physiologic sleep (Mamelak et al., *Biol Psych* 1977;12:273-288). Therefore, early investigators administered GHB to patients suffering from disorders of disturbed sleep, including narcolepsy (Broughton et al. in *Narcolepsy*, NY, NY: Spectrum Publications, Inc. 1976:659-668), where it was found to increase total nocturnal sleep time, decrease nocturnal awakenings and increase Stage 3-4 (slow wave) sleep. Three open-label and two placebo-controlled studies provided a body of evidence demonstrating that improvements in nocturnal sleep were associated with a reduction in cataplexy and improvements in excessive daytime sleepiness (Broughton et al., *Can J. Neurol Sci* 1979; 6:1-6, and Broughton et al., *Can J. Neurol Sci* 1980; 7:23-30).

An estimated 6 million Americans suffer the often baffling symptoms of fibromyalgia or chronic fatigue syndrome. Patients with fibromyalgia, also referred to as fibromyalgia

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syndrome, FMS or fibrositis syndrome, report widespread musculoskeletal pain, chronic fatigue, and non-restorative sleep. These patients show specific regions of localized tenderness in the absence of demonstrable anatomic or biochemical pathology, and patients suffering from fibromyalgia typically describe light and/or restless sleep, often reporting that they awaken feeling unrefreshed with pain, stiffness, physical exhaustion, and lethargy. See, H. D. Moldofsky et al., *J. Musculoskel. Pain*, 1, 49 (1993). In a series of studies, Moldofsky's group has shown that aspects of the patients' sleep pathology are related to their pain and mood symptoms. That is, patients with fibrositis syndrome show an alpha (7.5 to 11 Hz) electroencephalographic (EEG), non-rapid-eye-movement (NREM) sleep anomaly correlated with musculoskeletal pain and altered mood. Moldofsky has interpreted this alpha EEG NREM sleep anomaly to be an indicator of an arousal disorder within sleep associated with the subjective experience of non-restorative sleep. See H. D. Moldofsky et al., *Psychosom. Med.*, 37, 341 (1975).

Fibromyalgia patients frequently report symptoms similar to those of patients with post-infectious neuromyasthenia, also referred to as chronic fatigue syndrome (CFS). CFS is a debilitating disorder characterized by profound tiredness or fatigue. Patients with CFS may become exhausted with only light physical exertion. They often must function at a level of activity substantially lower than their capacity before the onset of illness. In addition to these key defining characteristics, patients generally report various nonspecific symptoms, including weakness, muscle aches and pains, excessive sleep, malaise, fever, sore throat, tender lymph nodes, impaired memory and/or mental concentration, insomnia, and depression. CFS can persist for years. Compared with fibromyalgia patients, chronic fatigue patients have similarly disordered sleep, localized tenderness, and complaints of diffuse pain and fatigue.

Scharf et al. conducted an open-label study to evaluate the effects of GHB on the sleep patterns and symptoms of non-narcoleptic patients with fibromyalgia (Scharf et al., *J Rheumatol* 1998; 25: 1986-1990). Eleven patients with previously confirmed diagnosis of fibromyalgia who reported at least a 3-month history of widespread musculoskeletal pain in all body quadrants and tenderness in a least 5 specific trigger point sites participated in the study. Results showed that patients reported significant improvements in the subjective assessments of their levels of pain and fatigue over all 4 weeks of GHB treatment as compared to baseline, as well as a significant improvement in their estimates of overall wellness before and after GHB treatment.

WO 2006/053186 to Frucht describes an open label study of 5 patients with hyperkinetic movement disorders including ethanol responsive myoclonus and essential tremor. Sodium oxybate, a sodium salt of GHB, was reported to produce dose-dependent improvements in blinded ratings of ethanol responsive myoclonus and tremor and was said to be tolerated at doses that provided clinical benefit.

XYREM® sodium oxybate oral solution, the FDA approved treatment for cataplexy and excessive daytime sleepiness associated with narcolepsy, contains 500 mg sodium oxybate/ml water, adjusted to pH=7.5 with malic acid. In man, the plasma half-life of sodium oxybate given orally is about 45 minutes and doses of 2.25 grams to 4.5 grams induce about 2 to 3 hours of sleep (See, L. Borgen et al., *J. Clin. Pharmacol.*, 40, 1053 (2000)). Due to the high doses required and very short half-life of sodium oxybate, optimal clinical effectiveness in narcolepsy typically requires dosing of the drug twice during the night, with

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administration typically recommended at 2.5 to 4 hour intervals. For each dose, a measured amount of the oral solution is removed from the primary container and transferred to a separate container where it is diluted with water before administration. The second dose is prepared at bed-

time and stored for administration during the night. Liang et al. (published U.S. patent application US 2006/0210630 A1) disclose administration of GHB using an immediate release component and a delayed release component. The delayed release component of the formulations taught in Liang et al., however, function in a pH dependent manner.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the delivery profile of sodium oxybate controlled release formulations as described herein.

FIG. 2 shows the delivery profile of integrated dosage forms as described herein having an immediate release component and a controlled release component.

FIG. 3 provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the coating weight of a functional coating.

FIG. 4 provides a graph further illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the coating weight of a functional coating.

FIG. 5 provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the amount of pore former included within a functional coating.

FIG. 6 provides a graph further illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the amount of pore former included within a functional coating.

FIG. 7 provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by varying the molecular weight of a pore former included within a functional coating.

FIG. 8 provides a graph illustrating that suitable controlled release profiles from dosage forms prepared according to the present description can be achieved even with functional coatings formed using different grades of the same base polymer material.

FIG. 9A and FIG. 9B provide graphs illustrating the effects of alcohol on the delivery profile of sustained-release formulations prepared as described herein.

FIG. 10 provides a graph illustrating the controlled release performance achieved by dosage forms as described herein having functional coatings prepared from aqueous dispersions of ethylcellulose as the base polymer.

FIG. 11 provides a graph illustrating the controlled release performance achieved by dosage forms as described herein incorporating calcium oxybate as the drug.

FIG. 12 provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein (Treatment B).

FIG. 13 provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein (Treatment C).

FIG. 14. provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium

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oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein dosed at 4 g (Treatment D) and 8 g (Treatment E).

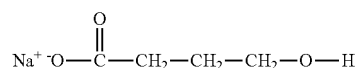
DETAILED DESCRIPTION

Formulations and dosage forms for the controlled release of a drug are described herein. Formulations described herein are suited to the controlled release of high dose drugs that are highly water soluble. In addition, in certain embodiments, the formulations described herein provide controlled release of drugs that are highly hygroscopic, even where such drugs must be administered at relatively high doses. In particular embodiments, the controlled release formulations are provided as a unit dosage form, and in one such embodiment, the controlled release formulation is provided as a coated tablet.

The formulations and dosage forms of the present invention can also include an immediate release component. The immediate release component can form part of a controlled release (CR) unit dosage form or may be a separate immediate release composition. Therefore, an immediate release (IR) component may be provided, for example, as a dry powder formulation, an immediate release tablet, an encapsulated formulation, or a liquid solution or suspension. However, the IR component may also be formulated as part of a single dosage form that integrates both the IR and CR components. In such an embodiment, the pharmaceutical formulation may be provided in the form of the coated tablet or capsule.

In specific embodiments, controlled release and immediate release formulations can be dosed together to a subject to provide quick onset of action, followed by maintenance of therapeutic levels of the drug substance over a sustained period of time. However, because the controlled release component and immediate release component described herein need not be present in a single dosage form, as it is used herein, the phrase "dosed together" refers to substantially simultaneous dosing of the controlled release and immediate release components, but not necessarily administration in the same dosage form. Dosing the controlled release and immediate release components together offers increased convenience, allowing patients to quickly achieve and maintain therapeutic levels of a drug over a sustained period of time, while reducing the frequency with which the drug must be dosed. Furthermore, dosing the controlled release and immediate release components together may avoid the disadvantages of dosing regimens and formulations that result in highly pulsatile plasma concentrations.

An example of a drug that may be used with the controlled release dosage forms described herein is GHB. It should be noted that embodiments of controlled release dosage forms comprising GHB, and other drugs, are presented herein for purposes of example only and not for purposes of limitation. The formulations and unit dosage forms provided herein can be utilized to achieve controlled release of GHB, as well as pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. Suitable salts of GHB include the calcium, lithium, potassium, sodium and magnesium salts. The structure of the sodium salt of GHB, sodium oxybate, is given as formula (I):



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Methods of making GHB salts are described, for example, in U.S. Pat. No. 4,393,236, which is incorporated herein by reference.

Formulating GHB into a unit dosage form presents various challenges, and such challenges are magnified in the context of formulating a unit dosage form providing controlled release of GHB. For instance, GHB is very soluble, generally requires a relatively high dose, has a low molecular weight, and exhibits a short circulating half-life once administered. Therefore, a controlled release unit dosage form of GHB should be configured to deliver large doses of drug over a prolonged period of time, while being acceptably sized for oral administration. However, controlled release formulations typically require the addition of significant amounts of excipients or rate controlling materials to control the delivery of drug, and the presence and need for such materials often limits the drug loading available for a given controlled release technology. Additionally, low molecular weight drugs, such as GHB, typically exhibit high permeability through films and matrices. Even further, high water solubility increases drug mobility and may preclude the use of some approaches utilized to achieved a controlled release dosage form.

Another challenge to achieving a formulation capable of delivering GHB over a sustained period of time is the fact that some forms of GHB, such as the sodium salt of GHB, sodium oxybate, are extremely hygroscopic. As used herein, the term "hygroscopic" is used to describe a substance that readily absorbs and attracts water from the surrounding environment. The hygroscopic nature of sodium oxybate presents significant challenges to the formulation, production, and storage of dosage forms capable of delivering sodium oxybate over a sustained period of time. Despite the challenges noted, formulations and unit dosage forms providing controlled release of GHB are described herein.

A. Controlled Release Formulations

As used herein, the term "controlled release" describes a formulation, such as, for example, a unit dosage form, that releases drug over a prolonged period of time. The controlled release compositions described herein may be provided as a unit dosage form suitable for oral administration. In each embodiment of the controlled release compositions described herein, the drug incorporated in such compositions may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB.

In certain embodiments, the controlled release compositions described herein are formulated as unit dosage forms that deliver therapeutically effective amounts of drug over a period of at least 4 hours. For example, controlled release unit dosage forms as described herein may be formulated to deliver therapeutically effective amounts of drug over a period selected from about 4 to about 12 hours. In specific embodiments, the controlled release dosage forms described herein deliver therapeutically effective amounts of drug over a period selected from about 4, about 5, about 6, about 7, about 8, about 9, about 10 hours, and about 12 hours. In other such embodiments, the controlled release dosage forms deliver therapeutically effective amounts of drug over a period selected from a range of about 4 to about 10 hours, about 5 to about 10 hours, about 5 to about 12 hours, about 6 to about 10 hours, about 6 to about 12 hours, about 7 to about 10 hours, about 7 to about 12 hours, about 8 to about 10 hours, and from about 8 to about 12 hours. In yet other embodiments, the controlled release dosage forms deliver therapeutically effective amounts of drug over a period selected from a range of about 5 to about 9 hours, about 5

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to about 8 hours, about 5 to about 7 hours, and about 6 to about 10 hours, about 6 to about 9 hours, and about 6 to about 8 hours.

The compositions described herein facilitate production of controlled release dosage forms that provide a substantially constant drug release rate. In one embodiment, the controlled release dosage forms may be formulated to deliver not more than approximately 30% of the drug initially contained within the controlled release dosage form in the first hour post-administration. When referencing the amount of drug initially contained in the controlled release dosage form or "initial drug content" of the controlled release dosage form, for purposes of the present description, such amount refers to the total amount of drug included in the controlled release composition prior to administration to a patient.

As is detailed herein, the controlled release dosage forms according to the present description include a controlled release component (also referred to as a controlled release "formulation") and, optionally, an immediate release component (also referred to as an immediate release "formulation" or an immediate release "coating"). In specific embodiments, the controlled release dosage forms described herein may be formulated to deliver drug to the gastro-intestinal tract at desired rates of release or release profiles. For example, in some embodiments, controlled release dosage forms as described herein are formulated to release to the gastro-intestinal tract not more than about 10% to about 60% of the drug initially contained within the controlled release component of the controlled release dosage form during the first two hours post-administration, and not more than about 40% to about 90% of the drug initially contained within the controlled release component of the controlled release dosage form during the first four hours post-administration. In other embodiments, controlled release dosage forms as described herein are formulated to release to the gastro-intestinal tract not more than about 40% of the drug initially contained within the controlled release component in the first hour post-administration, not more than about 60% of the drug initially contained within the controlled release component during the first two hours post-administration, and not more than about 90% of the drug initially contained within the controlled release component during the first four hours post-administration. In still other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 30% of the initial drug content in the controlled release component in the first hour post-administration, not more than about 60% of the initial drug content in the controlled release component during the first two hours post-administration, and not more than about 90% of the initial drug content of the controlled release component during the first four hours post-administration. In other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 50% of the initial drug content of the controlled release component during the first hour post-administration, between about 50 and about 75% of the initial drug content of the controlled release component after two hours, and not less than 80% of the initial drug content of the controlled release component after four hours post administration. In still other embodiments, a controlled release dosage form as described herein may be formulated release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component during the first hour post-administration, between about 5 and about 30% of the initial drug content of the controlled

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release component after two hours, between about 30% and about 50% of the initial drug content of the controlled release component after 4 hours, between about 50% and about 70% of the initial drug content of the controlled release component after 6 hours, and not less than about 80% of the initial drug content of the controlled release component after 10 hours post administration. In yet other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component after the first hour post-administration, between about 20% and about 50% of the initial drug content of the controlled release component after 2 hours, between about 50% and about 80% of the initial drug content of the controlled release component after 4 hours, and not less than 85% of the initial drug content of the controlled release component after 8 hours post-administration. The rate and extent of the absorption of GHB varies along the length of the GI tract with lower amounts absorbed in the more distal portions (i.e., the ileum and the colon).

Due to the rapid clearance of GHB from the plasma, when GHB is administered in an immediate release formulation, even large doses of the drug (e.g., a dose of between about 2.25 g and 4.5 g) generally result in plasma levels below 10 µg/mL within 4 hours of ingestion. In order to achieve therapeutic efficacy, therefore, a second, equal, dose is often required within 4 hours after administration of the first dose, and some patients may require administration of a second as soon as 2.5 hours after administration of the first dose. In such an instance, in order to maintain therapeutic efficacy, 4.5 g to 9 g of drug must be administered to the patient in two separate doses within 2 to 5 hours. This also requires that the second dose be administered during the night, which requires that the patient be awakened to take the second dose. The result is that the C_{max}/C_{min} ratio of GHB over an six hour period can be greater than 4 and is often greater than 8. In certain embodiments, for a given dose of GHB, administration of GHB using controlled release dosage forms as described herein can achieve a rapid rise in plasma concentrations of GHB, but with a prolonged duration of plasma levels above 10 µg/mL. In certain such embodiments, a GHB controlled release dosage form as described herein provides a C_{max} to C_{min} ratio of GHB over a prolonged period of time after administration selected from less than 3 and less than 2. Therefore, in specific embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a C_{max} to C_{min} ratio of GHB selected from less than 3 and less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours. For example, in particular embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a C_{max} to C_{min} ratio of GHB selected from less than 3 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours, while also providing GHB plasma concentrations of at least 10 µg/mL over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours. In still other embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a C_{max} to C_{min} ratio of GHB selected from less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours, while

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also providing GHB plasma concentrations of at least 10 µg/mL over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours.

Drug delivery performance provided by the dosage forms described herein can be evaluated using a standard USP type 2 or USP type 7 dissolution apparatus set to 37° C. ± 2° C. under the conditions described, for example, in the experimental examples provided herein. The dissolution media may be selected from dissolution media known by those of skill in the art such as at least one of purified water, 0.1N HCl, simulated intestinal fluid, and others.

In particular embodiments, the controlled release formulations described herein work to reduce inter patient variability in delivery of GHB. In particular, controlled release formulations described herein provide time dependent release of GHB over a sustained period of time. Previous references have described targeted release dosage forms of GHB that function in a pH dependent manner. However, due to inter-subject variability in gastrointestinal pH conditions, delivery of GHB from such dosage forms can be inconsistent. Moreover, because relatively high doses of GHB are typically required for therapeutic effect, unit dosage forms of GHB are also relatively large and may be retained for a period of time in the stomach, which can lead to intra- and inter-patient variability in dose delivery of GHB from pH dependent delivery systems due to variability in gastric retention time. Further, patients with fibromyalgia have an increased chance of also suffering from irritable bowel syndrome (see, e.g., *Fibromyalgia in patients with irritable bowel syndrome*. An association with the severity of the intestinal disorder, *Int J Colorectal Dis.* 2001 August; 16(4): 211-5.) Irritable bowel syndrome is also associated with delayed gastric emptying and variable gastric emptying (see, e.g., *Dyspepsia and its overlap with irritable bowel syndrome*, *Curr Gastroenterol Rep.* 2006 August; 8(4):266-72.) Therefore many patients with fibromyalgia and suffering from irritable bowel syndrome may experience more variability in gastric transit or prolonged gastric transit. By operating in a time dependent manner once placed in an aqueous environment, controlled release formulations described herein offer consistent GHB delivery characteristics and reduce the likelihood of undesirable intra- and inter-patient inconsistencies in dose delivery that may result from variances in gastric retention time that can occur between different patients and different patient populations.

Controlled release formulations described herein may be formulated to completely release a drug within a desired time interval. As has been reported, the bioavailability of GHB decreases in the lower GI, with bioavailability decreasing the lower the drug is delivered in the GI (See, e.g., U.S. Patent Publication No. US2006/0210630). Therefore, in certain embodiments, the controlled release dosage forms are provided that deliver substantially all the GHB contained therein over a sustained period of time that is long enough to increase patient convenience, yet short enough to reduce dosing of GHB in the lower GI. In specific embodiments, controlled release GHB dosage forms are provided that deliver approximately 90% or more of the GHB contained within the controlled release formulation within about 4 to about 10 hours of administration. For example, dosage forms for the controlled release of GHB as described herein may be formulated to deliver approximately 90% or more of the drug included within the controlled release formulation within about 4, 5, 6, 7, 8, 9, 10, or 12 hours of administration. In one such embodiment, a dosage form for the sustained delivery of GHB according to the present descrip-

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tion is formulated to deliver more than 90% of the GHB included within the controlled release formulation within 12 hours post-administration. Such embodiments serve to not only provide controlled release of GHB, but they also work to deliver GHB where bioavailability is highest, which can also provide increased dose consistency.

The controlled release dosage forms described herein may comprise a relatively high concentration of drug that can, in some instances, harm a patient if the formulation releases the drug at a rate that is faster than the intended sustained rate. This rapid release of the drug is sometimes referred to as "dose dumping." To avoid this potential danger, certain embodiments of the controlled release dosage forms described herein may comprise formulations that are resistant to dose dumping. Some users may intentionally attempt to increase the drug release rate of the controlled release dosage form using alcohol (e.g., potential abusers may take the controlled release dosage form prior to, simultaneously with, or after consuming an alcoholic beverage or, alternatively, may seek to extract the drug from the controlled release dosage form by placing the dosage form in solution containing alcohol). Other users may take the dosage form with alcohol, not necessarily in a manner considered abuse of the drug or alcohol, but without regard for the potential risks of dose dumping or contraindication of the two substances. In one embodiment, a controlled release dosage form as disclosed herein may include a coating composition that is resistant to alcohol or that does not dissolve substantially faster in alcohol. In one such embodiment, the controlled release dosage form may comprise the drug sodium oxybate and include a coating composition including ethylcellulose that is resistant to dose dumping in alcohol. In another embodiment, the controlled release dosage form may include a coating composition that is resistant to dose dumping after administration. For example, the controlled release dosage form may include a coating composition that is resistant to dose dumping in the GI tract after being exposed to gastric fluid and intestinal fluid.

In certain embodiments, the controlled release formulations described herein are provided as a coated tablet composition having a controlled release core coated by a functional overcoat. The composition of the controlled release core provided in such embodiments facilitates high drug loading, thereby, rendering the coated tablet suitable for formulation and sustained delivery of drugs administered at high doses. The functional overcoat works to control delivery of drug from the controlled release core and maintain the structural integrity of the dosage form over time. In addition to the controlled release core and functional overcoat, the coated tablet composition as described herein may further include a moisture barrier or cosmetic coating disposed over the functional overcoat.

I. Controlled Release Component

Where the controlled release formulations described herein are formulated as a coated tablet having a controlled release core (CR core), the CR core includes at least one drug substance to be delivered from the controlled release dosage form. The drug included in the CR core may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. Examples of suitable salts of GHB include the calcium, lithium, potassium, sodium and magnesium salts. The CR core is formulated and configured to be suitable for oral administration. In one embodiment, coated tablets as described herein may be administered to provide a dose of GHB or a pharmaceutically acceptable salt, hydrate, tautomer, solvate or complex of GHB in a range of about 500

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mg to about 12 g of drug in one or more tablets. In particular embodiments, a CR core included in a controlled release dosage form according to the present description may include an amount of drug selected from about 100 mg to about 2,000 mg. In some such embodiments, the amount of drug included in the CR core may be selected from up to about 250 mg, 400 mg, 500 mg, 600 mg, 700 mg, 750 mg, 800 mg, 900 mg, 1,000 mg, 1,100 mg, 1,200 mg, 1,400 mg, 1,500 mg, 1,600 mg, 1,700 mg, 1,800 mg, 1,900 mg, and 2,000 mg. In certain such embodiments, the amount of drug included in a CR core as described herein may range from about 500 mg to about 2,000 mg, such as, for example, about 500 mg to 1,000 mg, about 600 mg to 1,000 mg, about 600 mg to 900 mg, about 600 mg to 800 mg, about 700 mg to 1,000 mg, about 700 mg to 900 mg and about 700 mg to 850 mg. In other such embodiments, the amount of drug included in a CR core as described herein may range from about 700 mg to about 2,000 mg, such as, for example, about 700 mg to 1,500 mg, about 700 mg to 1,400 mg, about 700 mg to 1,300 mg, about 700 mg to 1,200 mg, about 700 mg to 1,100 mg, about 700 mg to 1,000 mg, about 700 mg to 900 mg, and about 700 mg to 850 mg.

In one embodiment, the controlled release dosage form comprises a CR core wherein the relative amount drug in the CR core is at least 90% or greater by weight. In another embodiment, the relative amount of drug in the CR core ranges from between about 90% and 98%, about 91% and 98%, about 92% and 98%, about 93% and 98%, about 94% and 98%, about 95% and 98%, about 96% and 98%, and between about 97% and 98% by weight of the CR core. In yet another embodiment, the relative amount of drug in a CR core may be present at an amount selected from about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, and 98% by weight of the CR core. In certain such embodiments, the amount of drug in the CR core may range from about 94 to 98%, 94 to 97%, 94 to 96%, 95 to 98%, 95 to 97%, and 95 to 96.5% by weight of the CR core.

In one embodiment, the controlled release dosage form comprises a CR core that includes drug substance in combination with one or more excipients, such as binders, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, lubricants, glidants, or other suitable excipients. In one embodiment, a CR core as disclosed herein can include one or more binders that are known for use in tablet formulations. In one such embodiment, a CR core may include at least one binder selected from hydroxypropyl cellulose (HPC), ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate. In specific embodiments, the CR core included in a controlled release dosage form as disclosed herein may comprise binder levels ranging from approximately 1% to 10% by weight. For example, the CR core may include a binder in an amount selected from about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, and 10% by weight. In certain such embodiments, the amount of binder included in the CR core may range from about 1 to 2%, 1 to 3%, 1 to 4%, 1 to 5%, 1 to 6%, 1 to 7%, 1 to 8%, 1 to 9% and 1 to 10% by weight.

The CR core may include one or more lubricants to improve desired processing characteristics. In one embodiment, the CR core may include one or more lubricants selected from at least one of magnesium stearate, stearic

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acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added to the CR core in a range of about 0.5% to 5% by weight. In particular embodiments, a CR core as disclosed herein may comprise a lubricant in a range of about 0.5% to 2% by weight, about 1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in the CR core in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight. Still lower lubricant levels may be achieved with use of a “puffer” system during tableting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation.

The CR core may also include one or more surfactants. In certain embodiments, the CR core may include a tableted composition that may comprise one or more surfactants selected from, for example, ionic and non-ionic surfactants. In one such embodiment, CR core may include at least one anionic surfactant, including docusate sodium (dioctyl sulfosuccinate sodium salt) and sodium lauryl sulfate. In yet another embodiment, the CR core may include at least one non-ionic surfactant selected from including polyoxyethylene alkyl ethers, polyoxyethylene stearates, poloxamers, polysorbate, sorbitan esters, and glyceryl monooleate. In specific embodiments, one or more surfactants included in a CR core as disclosed herein may be present, for example, in an amount of up to about 3.0% by weight of the CR core. For example, in certain embodiments, the CR core may include one or more surfactants present in a range selected from about 0.01% to 3%, about 0.01% to 2%, about 0.01% to 1%, about 0.5% to 3%, about 0.5% to 2%, and about 0.5% to 1% by weight of the CR core.

The CR core included in controlled release dosage form as disclosed herein may also include fillers or compression aids selected from at least one of lactose, calcium carbonate, calcium sulfate, compressible sugars, dextrates, dextrin, dextrose, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, powdered cellulose, and sucrose. In another embodiment, a CR core may be prepared by blending a drug and other excipients together, and the forming the blend into a tablet, caplet, pill, or other dosage form according to methods known by those of skill in the art. In certain embodiments, a controlled release formulation as described herein may comprise a solid oral dosage form of any desired shape and size including round, oval, oblong cylindrical, or triangular. In one such embodiment, the surfaces of the CR core may be flat, round, concave, or convex.

The CR core composition included in a controlled release formulation provided as a coated tablet dosage form as described herein may be manufactured using standard techniques, such as wet granulation, roller compaction, fluid bed granulation, and direct compression followed by compression on a conventional rotary tablet press as described in Remington, 20th edition, Chapter 45 (Oral Solid Dosage Forms).

II. Functional Coating Composition

Where the controlled release formulations as described herein are provided as a coated tablet composition, the CR core is coated with a functional coating. The coating composition works to preserve the integrity of the unit dosage form post administration and serves to facilitate controlled release of drug from the CR core. In certain embodiments,

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the coating composition is formulated to facilitate controlled release of a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. In one such embodiment, the coating composition is sufficiently robust to preserve the integrity of the coated tablet pre- and post-administration, yet is subject to disintegration or crushing as it passes through a patient’s gastrointestinal tract and after all or substantially all the drug substance contained within the controlled release formulation has been delivered. Such a feature reduces the risk that bezoars formed from intact dosage form shells will form or be maintained within the GI tract of a patient, which may be of particular concern where the drug to be delivered must be administered at high doses using multiple unit dosage forms.

In one embodiment, a functional coating composition as disclosed herein may control, at least in part, the rate of release of the drug to be delivered from the CR core into the gastrointestinal tract. In one embodiment, the functional coating composition provides a functional coat that partly or fully covers the CR core included in the controlled release dosage form. In one embodiment, the functional coating composition as disclosed herein may include a polymer or blends of compatible polymers that are water soluble or that are water insoluble and selected to exhibit desired permeability characteristics. In one embodiment, the functional coating composition has a permeability that may be adjusted according to the solubility of the drug used in the CR core. In one such embodiment, the functional coating composition may comprise one or more water insoluble polymers that may swell but do not substantially dissolve in the GI tract. For example, in particular embodiments, a functional coating composition as disclosed herein may comprise a rate-limiting film that includes at least one of ethylcellulose, cellulose acetate, such as CA-398. In other embodiments, the functional coating may include combinations of ethylcellulose with ammonio methacrylate copolymers, such as EUDRAGIT RS, EUDRAGIT RL, and combinations thereof. Suitable ethylcellulose materials are readily commercially available, and include, for example, ETHOCEL ethylcellulose polymers. Where ethylcellulose is used to form the functional coating, the physical characteristics of the coating composition and residual shell may be modified by adjusting the molecular weight of the ethylcellulose. For example, different grades of ethylcellulose, including, but not limited to, 4 cP, 7 cP, 10 cP, and 20 cP grades, may be used to achieve a coating composition having desired physical characteristics.

A functional coating composition as disclosed herein may include one or more base polymer and at least one pore-former. In one embodiment, the base polymer content may range from about 50% to about 80% by weight of the coating composition. In certain embodiments, the base polymer may be present in an amount ranging from about 50% to 75%, about 55% to 75%, about 60% to 75%, and about 65% to 75% by weight of the coating composition. In one such embodiment, the base polymer may be present in an amount selected from about 50%, 55%, 60%, 65%, 70%, 75%, and 80% by weight of the coating composition. In cases where a filler material is used (e.g., insoluble, non film-forming material such as magnesium stearate, talc, or fumed silica), these limits apply to the composition of the remaining non-filler components in the film.

The permeability of the base polymer included in a functional coating as described herein may be modified by including a pore former in the base polymer. In one such embodiment, the functional coating composition including the pore former may be obtained by combining the pore

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former with the base polymer material in solution according to conventional techniques. A pore former as disclosed herein may include at least one polymeric pore former, such as hydroxyalkyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycols, polyvinyl alcohol, povidone, copovidone, and poloxamers, such as 188 or 407. In one embodiment, a pore former as disclosed herein may include at least one small-molecule pore former, such as a water soluble sugar or organic acid, including, for example, citric acid or sorbitol. In one such embodiment, a small-molecule pore former may be water soluble active agent, such as a pharmaceutically acceptable salt of GHB. In yet another embodiment, the pore former may comprise a polymer that expands in the presence of the drug included in the CR core, wherein expansion of the pore former may cause an increase in permeability of the functional coating composition. For example, in some embodiments, the functional coating composition may comprise a pore former that that expands or swells in the presence of sodium oxybate. In one such embodiment, the pore former includes a suitable carbomer.

Where used in the functional coating composition, a pore former or a pore-forming agent can be selected to modify the permeability of the coating composition provided over the CR core. For example, the permeability of the functional coating composition may be increased by including one or more pore formers or pore-forming agents in the coating composition. In one embodiment, the pore formers disclosed herein may be soluble in water. In one such embodiment, when a CR dosage form comprising a functional coating composition with at least one pore former is swallowed by a patient and contacted with gastric fluid, the water-soluble pore formers may dissolve and form pores or channels in the coating through which the drug is released. It is possible to use an enteric component as part or all of the pore former in the coating composition. Examples of such materials that may be used as a pore former in the context of the present description include cellulose acetate phthalate, methacrylic acid-methyl methacrylate copolymers, and polyvinyl acetate phthalate. However, incorporating enteric components in the film may result in delivery characteristics that exhibit some level of sensitivity to gastric and intestinal transit times.

Where included, the amount and nature of the pore former included in the functional coating composition can be adjusted to obtain desired release rate characteristics for a given drug substance. In one embodiment, the functional coating composition may include an amount of pore former that ranges from about 20% to about 50% by weight of the coating composition. For example, the pore former may be present in an amount ranging from about 20% to 45%, about 25% to 45%, about 30% to 45%, and about 35% to 45% by weight of the functional coating composition. In one such embodiment, the pore former may be present in an amount selected from about 20%, 25%, 30%, 35%, 40%, 45%, and 50% by weight of the functional coating composition.

The functional coating composition as disclosed herein may also comprise one or more plasticizers. In certain embodiments, the functional coating composition may include a plasticizer such as triethyl citrate or dibutyl sebacate. In one such embodiment, a plasticizer may be present in the functional coating composition in an amount ranging from about 5% to 15% by weight relative to the base polymer. In certain embodiments, the functional coating composition may include a plasticizer in an amount selected from about 5%, 8%, 10%, 12%, and 15% by weight relative to the base polymer.

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The functional coating composition as disclosed herein may also include an anti-tack agent. For example, certain embodiments of the functional coating composition may include an anti-tack agent selected from one or more of talc, glyceryl monostearate, and magnesium stearate. Many of the anti-tack agents are also suitable fillers. Addition of fillers, especially magnesium stearate, is one way to make the film more brittle and the dosage form more prone to crushing as it transits through the GI. Depending on forces encountered in the GI, varying the filler level in the film may allow one to adjust the duration, or extent of drug delivered, at which breach of the film and abrupt release of remaining contents occurs.

The functional coating composition as disclosed herein may be applied to a CR core at a weight that facilitates a suitable combination of sustained drug release and dosage form structural integrity. In certain embodiments, the functional coating composition may be applied at a weight of about 10 to about 100 mg. In particular embodiments, for example, the functional coating may be applied at a weight selected from about 20 to 60 mg, about 20 to 50 mg, about 20 to 40 mg, about 20 to 30 mg, about 30 to 60 mg, about 30 to 50 mg, about 30 to 40 mg, about 40 to 60 mg, about 40 to 50 mg, and about 50 to 60 mg. These ranges are useful for oval tablets of about 500 mg to about 1000 mg in weight. Alternatively, for a given tablet size or weights, the functional coating composition as disclosed herein may be applied at between about 2.5% and 7.5% of the tablet weight. For example, in one such embodiment, where the tablet is a 2,000 mg oval tablet, a functional coating composition may be applied at a weight ranging from about 50 mg to about 150 mg.

In addition to adjusting the amount or nature of the pore former included in the functional coating composition, the release rate of drug provided by the controlled release dosage form disclosed herein may be adjusted by modifying the thickness or weight of the functional coating composition. For example, a more rapid release rate will generally be achieved as the amount of a given pore former included in the functional coating composition is increased or the thickness or weight of the coating composition applied over the CR core is decreased. Conversely, a slower or more controlled release may be achieved, generally, as relatively less of a given pore former is included in the functional coating composition or the thickness or weight of the coating composition applied to the CR core is increased. Additionally, in certain embodiments, the release rate of drug from the CR core may be adjusted by modifying the water content of the functional coating composition. For example, increasing the water content of the functional coating composition may increase the release rate of drug the CR core.

The functional coating compositions as disclosed herein may be applied to a CR core according to conventional coating methods and techniques. In one embodiment, the functional coating composition as disclosed herein may be applied using a conventional perforated pan coater. In another embodiment, the functional coating composition may be applied using an aqueous pan-coating process. In one such embodiment, the use of an aqueous pan-coating process may include the use of a latex dispersion. For example, a latex dispersion such as SURELEASE may be used for an ethylcellulose pan-coating process. In another example, a latex dispersion such as EUDRAGIT RS 30 D may be used in a pan-coating process for ammonio-methacrylates. In yet another embodiment, the functional coating composition may be applied using a solvent-based pan-coating process. In one such embodiment, a solvent-based

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pan-coating process may include the use of an alcohol solvent, such as ethanol. For example, an alcohol-solvent based pan-coating process may utilize a 95% ethanol and 5% water (w/w) solvent.

In one embodiment, the functional coating compositions as described herein may be applied using a fluid bed coating process such as a Wurster fluid bed film coating process. In another embodiment, the functional coating composition may be applied using a compression coating process. In yet another embodiment, the functional coating composition may be applied using a phase inversion process. In certain embodiments, the functional coating composition as disclosed herein may be applied over a suitable subcoating.

III. Moisture Barrier/Cosmetic Coatings

When a controlled release formulation or dosage form is provided as a coated tablet, in some embodiments, it may be coated with a moisture barrier or a moisture-resistant coating composition. For example, a controlled release dosage form as disclosed herein comprising GHB as the drug substance may include a moisture barrier. In another example, a moisture barrier may be particularly useful where sodium oxybate is used as the drug substance. In one embodiment, the moisture barrier may be a polyvinyl alcohol-based coating, such as OPADRY AMB (Colorcon Inc., Harleysville, Pa.). In another embodiment, the moisture barrier may be a hydroxypropyl methylcellulose (HPMC)/wax-based coating, such as AQUARIUS MG (Ashland Aqualon, Wilmington, Del.). In yet another embodiment, the moisture barrier may be a HPMC/stearic acid-based coating. The moisture barrier as disclosed herein, in some embodiments, may be formed using a reverse enteric material, such as EUDRAGIT E, and may be coated from alcohol or alcohol/water solutions or from an aqueous latex dispersion. In embodiments where the controlled release dosage form is provided as a tablet of about 500 mg-1000 mg in weight, for example, the moisture barrier coating may be applied at a weight selected from about 10 mg to about 60 mg/tablet and about 25 mg to about 50 mg/tablet. In general, a minimum weight is needed to ensure complete coverage of the tablet in light of imperfections in the tablet surface, and a maximum weight is determined by practical considerations, such as coating time, or by the need for better moisture protection.

As will be readily appreciated, the controlled release dosage form can be further provided with a cosmetic top coat. In one embodiment, a top-coat may be applied to an existing coating composition such as a moisture barrier. In certain embodiments, a cosmetic top-coat may include at least one of HPMC and copovidone. For example, when the controlled release dosage form includes a coated tablet comprising sodium oxybate as the drug, a top-coat including HPMC, such as for example an HPMC material selected from one or more of HPMC E3, E5, or E15, may be applied over a moisture barrier to improve the effectiveness of the moisture barrier by reducing any seepage of sodium oxybate and water from the surface of the coated tablet.

B. Immediate Release Formulations

The controlled release formulations described herein can be dosed together with an immediate release (IR) formulation. In one embodiment, the IR formulation may be provided as a separate formulation or dosage form that may be dosed together with a dosage form provided by a controlled release dosage form as described herein. The IR formulation may be provided in any suitable form, such as a dry powder formulation, a tablet or capsule unit dosage form, or a liquid formulation such as a solution or suspension formulation. As used herein, "immediate release" refers to a drug formulation that releases more than about 95% of the drug contained

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therein within a period of less than one hour after administration. In particular embodiments, the IR component of the compositions described herein release more than about 95% of the drug contained therein within a period selected from less than 45 minutes, less than 30 minutes, and less than 15 minutes post-administration. In other embodiments, the IR component of the compositions described herein release more than about 80% of the drug contained therein within a period selected from less than 45 minutes, less than 30 minutes, and less than 15 minutes post-administration.

In certain embodiments, the IR formulation is provided as an immediate release component of a controlled release dosage form as described herein. In one such embodiment, the IR component is provided as a coating over a controlled release component or formulation as described herein. A unit dosage form that integrates both controlled release and immediate release components can increase the convenience and accuracy with which a drug such as GHB is dosed to patients by providing a unit dosage form that not only provides quick onset of action, but also sustained delivery of GHB to the patient over a prolonged period of time. Furthermore, where the drug to be delivered is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, dosing controlled release and immediate release formulations together may avoid the disadvantages of the current GHB dosing regimens, which can result in highly pulsatile plasma concentrations.

I. Immediate Release Component

When the immediate release formulation is provided as an integrated IR component of a controlled release dosage form, the amount of drug included in the IR component may range from about 10% to 50% by weight of the total drug included in the integrated dosage form. As used herein, "integrated dosage form" refers to a single unit dosage form that includes both immediate release and controlled release components as described herein. For example, where the drug to be delivered from the immediate release and controlled release formulations incorporated into an integrated dosage form is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB in some embodiments, the drug included in the IR component may comprise about 10% to about 50% by weight of the total drug included in the unit dosage form. In one such embodiment, the drug included in the IR component of an integrated dosage form may comprise about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by weight of the total drug included in the unit dosage form. For example, an integrated dosage form as described herein may contain 1000 mg sodium oxybate, wherein 100 mg to 500 mg sodium oxybate (10% to 50% by weight) is contained within and delivered from the IR component and 500 mg to 900 mg sodium oxybate (50% to 90% by weight) is contained within and delivered from the CR component.

Where the IR component is provided as a coating over a controlled release dosage form, in certain embodiments, the drug included in the IR component may account for between about 75% and 98% by weight of the IR formulation. In the context of describing an IR component provided over a controlled release dosage form as described or disclosed herein, the controlled release dosage forms referred to include the controlled release formulations described herein, including, in specific embodiments, CR cores coated with a functional coating as described herein. Again, the drug included in such an embodiment may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. In certain embodiments,

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the IR component may comprise sodium oxybate in an amount of selected from a range of between about 75% and 98%, between about 80% and 98%, between about 85% and 98%, between about 90% and 98%, and between about 95% and 98% by weight.

An IR component formed as a coating over a controlled release dosage form as disclosed herein may be applied as a tableted overcoat according to conventional tablet coating and binding methods. Alternatively, an IR component formed as a coating over a controlled release dosage form as disclosed herein may be applied as a film coating, such as, for example, from a solution containing a suitable amount of drug and film former. In one such embodiment, wherein sodium oxybate is the drug included in the IR component, the coating forming the IR component may be coated over a controlled release dosage form from a coating solution that utilizes an alcohol and water solvent. For example, a suitable immediate release coating may be formed using a 20% solution of sodium oxybate in a 60%/40% (w/w) alcohol/water solution that contains a suitable film-former.

Where the IR component is provided as a film coat and includes one or more film-formers, suitable film formers may be selected from, for example, copovidone, hydroxypropyl cellulose, HPMC, and hydroxymethyl cellulose materials. An IR component containing sodium oxybate as the drug can be applied as a suspension or as a solution by adjusting the water content of the coating mixture. For a suspension, little or no water is added to the alcohol, and the example film formers should be suitable. To prepare a solution, however, the water content of the solvent is increased, for example to 40%, and a smaller set of film formers would be suitable due to the precipitation of most common film formers in the presence of sodium oxybate solution. Hypromellose is one of several potential film formers that is suitable. It is further possible, with more difficulty, to apply the sodium oxybate from an aqueous solution; however, the same limitations on film former applies, and processing is complicated by the hygroscopic nature of the drug. In one embodiment, the IR component useful for use in a controlled release dosage form as described herein includes 91% sodium oxybate and 9% hypromellose (HPMC E-15) that is applied from a solution containing 20% sodium oxybate and 2% HPMC E-15 in a 60/40 w/w ethanol/water solvent.

Where the IR component of an integrated dosage form is provided as a coating over the controlled release dosage form, the coating forming the IR component may further include one or more of an anti-tack agent and a plasticizer to facilitate processing and to improve film properties. Furthermore, addition of one or more surfactants, such as sodium lauryl sulfate, may improve the dissolution of IR coatings that contain hydrophobic components (such as anti-tack agents or water-insoluble film formers).

In embodiments where the IR component is provided as a coating over a controlled release formulation as described herein, the IR component may be positioned directly over the functional coating of the controlled release formulation. Where desired or necessary based on the drug to be delivered from the IR component and controlled release formulation included in such an integrated dosage form, the outer surface of the IR component may then be coated with a moisture barrier layer. For example, where the drug delivered by the integrated dosage form is highly hygroscopic, such as, for example, sodium oxybate, a moisture barrier layer over the immediate release coating forming the IR component may be provided.

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The formulation and structure of integrated dosage forms as described herein can be adjusted to provide a combination of immediate release and controlled release performance that suits a particular dosing need. In particular, the formulation and structure of integrated dosage forms as described herein can be adjusted to provide any combination of the immediate release and controlled release performance characteristics described herein. In particular embodiments, for example, the drug delivered from an integrated dosage form as described herein is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, and the integrated dosage form sustains delivery of GHB over a period of from about 4 to about 10 hours. In one such embodiment, the IR component of the integrated dosage form provides rapid onset of action, releasing more than about 90% of the drug contained therein within a period of time selected from less than one hour, less than 45 minutes, less than 30 minutes and less than 15 minutes after administration, while the controlled release composition included in the integrated dosage begins to deliver drug as the IR component is released and continues to deliver drug for a sustained period of between about 4 and about 10 hours. In another such embodiment, the IR component of the integrated dosage form provides rapid onset of action, releasing more than about 90% of the drug contained therein within a period of time selected from less than one hour, less than 45 minutes, less than 30 minutes and less than 15 minutes after administration, while the controlled release composition included in the integrated dosage begins to deliver drug after the IR component is released and continues to deliver drug for a sustained period of between about 4 and about 10 hours.

Moreover, the ratio of drug release from the IR component and CR component can be adjusted as needed to facilitate a desired dosing regimen or achieve targeted dosing. A dosage form as described herein that integrates both IR and CR components may be formulated to deliver as much as 2,000 mg of a desired drug, such as GHB or a pharmaceutically acceptable salt, hydrate, tautomer, solvates or complex of GHB. In particular embodiments, the total amount of drug contained within an integrated IR/CR dosage form according to the present description may be between about 500 mg and about 1,400 mg. For example, in certain such embodiments, the total amount of drug may be selected from between about 500 mg and 1,400 mg, about 500 mg and 1,200 mg, about 500 mg and 1,100 mg, about 600 mg and 1,200 mg, about 600 mg and 1,100 mg, about 600 mg and 1,000 mg, about 600 mg and 950 mg, about 600 mg and 850 mg, about 600 mg and 750 mg, about 750 mg and 1,200 mg, about 750 mg and 1,100 mg, about 750 mg and 1,000 mg, about 750 mg and 950 mg, and about 750 mg and 850 mg. In an integrated IR/CR dosage form, the relative amounts of drug delivered from the IR component and CR components may be adjusted as desired as well. In particular embodiments, the ratio of drug released from the IR component to drug released from the CR component is from about 1:2 to about 1:4. In certain embodiments, such ratio is selected from about 1:2, 1:2.5, 1:3, 1:3.5 and 1:4.

In particular embodiments, the integrated dosage form may be formulated such that the controlled release formulation begins release of drug substantially simultaneously with delivery of the drug from the IR component. Alternatively, the integrated dosage form may be formulated such that controlled release formulation exhibits a start-up time lag. In one such embodiment, for example, the integrated dosage form maybe formulated and configured such that start-up of delivery of drug from the controlled release

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composition occurs after delivery of drug from the IR component is substantially complete. Where a start-up lag time is desired, an enteric coating may be applied over the controlled release component (e.g., over a functional coating), but such a coating would necessarily limit the start-up lag to gastric residence and its associated variability. Use of enteric pore-formers would also impart a start-up lag, and such an embodiment would be more sensitive to food effects and gastric motility. Where a less pH-sensitive start-up lag time is desired, the delay may be accomplished or adjusted by the use of one or more coatings and films, including the functional coating provided over a CR core and, where utilized, the moisture barrier or cosmetic overcoats. In particular, start-up lag time as disclosed herein may be adjusted by modifying the formulation, thickness, and/or weight of the functional coating provided over the CR core, the moisture barrier layer or one or more non-functional or cosmetic overcoats.

EXAMPLES

Example 1—Controlled Release Core

A granulation used to form CR cores as described herein was manufactured in a 25 L high shear granulator according to the formula in Table 1A. Klucel EXF was divided into two equal portions; half of the Klucel EXF was dissolved in the ethanol, and half was dry blended with sodium oxybate. The material was initially granulated with 10% w/w ethanol and then titrated with another 3.5% w/w ethanol solution to achieve desired granule growth. A suitable wet mass was obtained at a total ethanol concentration of 13.5% w/w. The wet granules were divided into two sub lots and then each sub lot was dried in a 5-liter Niro fluid bed dryer. The dried granules were combined and milled through a COMIL

equipped with a 14 mesh screen. Granulation parameters and particle size distribution are shown in Tables 1B and 1C, respectively.

The granulation was then combined with 2% magnesium stearate lubricant, and tablets were compressed on a 16-station press fitted with chrome-plated 0.325"×0.705" modified oval tooling. The average tablet hardness was 10.7 kiloponds.

TABLE 1A

Controlled Release Core Tablet Formulation			
Ingredient(s)		% w/w	mg/tablet
1	Sodium Oxybate	96.0	750.0
2	Hydroxypropyl cellulose, NF (Klucel EXF)	2.0	15.6
3	Ethanol, USP (200 proof)*	13.5	
4	Magnesium Stearate, NF	2.0	15.6
TOTAL		100.0	781.2

*Granulation solvent, removed during drying step

TABLE 1B

Granulation Parameters WET GRANULATION	
GRANULATION SOLUTION	250
ADDITION RATE (G/MIN)	
TOTAL GRANULATION TIME (INCLUDING SOLUTION ADDITION AND WET MASSING TIME)	7 MINUTES

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TABLE 1B-continued

Granulation Parameters WET GRANULATION		
IMPELLER SPEED (RPM)	300	
CHOPPER SPEED (RPM)	1800	
DRYING	SUBLOT 1	SUBLOT 2
DRYING INLET	70	70
TEMPERATURE (° C.)		
TOTAL DRYING TIME (MIN)	17	18
EXHAUST TEMPERATURE	47	48
AT END OF DRYING (° C.)		
LOD (% WT LOSS)	0.84	0.92

TABLE 1C

Screen Analysis of Milled Granulation			
Screen size US Std mesh	Opening size microns	Wt Retained (%)	
20	850	2.1	
40	420	10.4	
60	250	19.8	
80	180	25.0	
120	125	22.9	
200	75	12.5	
Pan	<45	7.3	

Example 2—Functional Coating

Tablets from Example 1 were coated with a solution prepared according to the formulation in Table 2A. The ethylcellulose was first added to a 95/5 w/w mixture of ethanol and water and stirred until dissolved. Next, the hydroxypropyl cellulose and dibutyl sebacate were added and stirred until completely dissolved. 4.7 kg of tablets from Example 1 were then charged to an 8" pan Driam tablet coater and coated with the solution to 5.1 wt % gain (40 mg/tablet). The tablets were then dried for 5 minutes in the coater, and then finally cooled in the pan to an exhaust temperature below 30° C.

The dissolution profile was measured in de-ionized water using USP Apparatus 2 set to 37° C.±2° C. with paddles at 50 rpm. Samples were analyzed by HPLC. As shown in FIG. 1, the coated tablets exhibited controlled release with duration of approximately 6 hours. The dosage form released 12% of its contents after 1 hour, 34% after 2 hours, 71% after 4 hours, 93% after 6 hours, and 99% after 8 hours.

TABLE 2A

Formulation of Sodium Oxybate Sustained-Release Tablets			
Ingredient(s)	% of coat solids	% w/w of tablet	mg/ tablet
5 Sodium Oxybate tablet core		95.13	781.25
6 Hydroxypropyl cellulose, NF (Klucel EF)	37.0	1.80	14.80
7 Dibutyl sebacate	5.0	0.24	2.00
65 8 Ethylcellulose, NF (Ethocel Standard Premium 10)	58.0	2.82	23.20

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TABLE 2A-continued

Formulation of Sodium Oxybate Sustained-Release Tablets			
Ingredient(s)	% of coat solids	% w/w of tablet	mg/tablet
9 Ethanol, USP (200 proof)*			
10 Purified water*			
TOTAL	100.0	100.00	821.25

*Coating solvent, removed during processing

TABLE 2B

Coating Parameters for Driam 8" Pan Coater		
CR COATING	AVERAGE	RANGE
INLET TEMPERATURE (° C.)	46	42-55
EXHAUST TEMPERATURE (° C.)	43	41-46
INLET AIRFLOW (PASCAL)	>300	>300
ATOMIZATION PRESSURE (BAR)	2	2.0
SPRAY RATE (G/MIN)	35	32-37
PAN SPEED (RPM)	6	5-7

Example 3—Immediate-Release Overcoat

A solution of 20% sodium oxybate as active and 2.0% hypromellose E-15 (HPMC E-15) as film-former was prepared in 60/40 (w/w) ethanol/water. The coating solution was manufactured by first dissolving the HPMC E15 in water, then adding the ethanol and sodium oxybate. 3 kg of 750-mg strength sustained-release tablets from Example 2 were charged to a Driam tablet coater equipped with an 8" pan and preheated to 40° C. The entire coating solution was applied according to the parameters listed in Table 3A. The tablet weight gain was monitored every 5 minutes, and the coating was stopped when the entire solution was sprayed (the theoretical weight gain is 33.5%). The tablets were dried for 15 minutes; the tablets did not lose any weight during the 15 minute drying time, and so it was assumed that the drying was complete. The tablets were then cooled in the pan to an exhaust temperature of <30° C.

Analysis by HPLC revealed an overall potency of 961 mg, and thus a drug overcoat potency of 211 mg. Dissolution testing using USP Apparatus 2 set to 37° C.±2° C. with paddles at 50 rpm, shown in FIG. 2, demonstrates substantially the entire immediate-release overcoat is dissolved in 15 minutes and that controlled release is maintained for approximately 6 hours thereafter. Higher amounts of drug can be applied to the immediate release overcoat by using higher amounts of coating solution and extending the coating time accordingly.

TABLE 3A

Parameters for Immediate-Release Overcoating with 8" Driam Coater		
DRUG OVER-COATING	AVERAGE	RANGE
INLET TEMPERATURE (° C.)	59	55-63
EXHAUST TEMPERATURE (° C.)	51	50-53
PRODUCT TEMPERATURE (° C.)	43	41-49
INLET AIRFLOW (PASCAL)	>300	>300
ATOMIZATION PRESSURE (BAR)	2	2
SPRAY RATE (G/MIN)	16	14-17
PAN SPEED (RPM)	8	7-8

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TABLE 3A-continued

Parameters for Immediate-Release Overcoating with 8" Driam Coater		
DRUG OVER-COATING	AVERAGE	RANGE
TOTAL RUN TIME (HRS)	4 HRS 47 MIN (COATING) 15 MIN (DRYING)	

The following examples illustrate aspects of the sustained-release coating formulation with several evaluations using tablets from Example 1.

Example 4—Effect of Membrane Weight with Poloxamer as Pore Former in Functional Coating

One means of controlling dissolution is by adjustment of the coating thickness, or amount of film applied to each tablet. This was illustrated with a film consisting of 33% poloxamer 188 (P188) and 67% ethylcellulose 10 cPs (EC-10). The coating solution was prepared by dissolving 3.59 grams of EC-10 and 1.77 grams of P188 in a mixture of 80 grams denatured alcohol ("alcohol") and 4 grams de-ionized water. (Denatured alcohol, S-L-X manufactured by W. M. Barr, is approximately a 50/50 w/w blend of methanol and ethanol.)

Twelve tablets from Example 1 were coated in a Caleva Mini-coater/Drier 2 under parameters listed in Table 4A. Periodically, the tablets were removed and weighed to determine film weight. Three tablets were removed at times corresponding to 21 mg, 30 mg, 40 mg, and finally 60 mg weight gain.

The dissolution profiles were measured with USP Apparatus 7 (Vankel Bio-dis) set to 37° C.±2° C. and using a dipping rate of 30/minute, tablets fixed in plastic holders and intervals corresponding to 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, and 14 h (each interval is 50 ml volume). The tubes were analyzed by conductivity, and results are calculated as percent of total amount. The results demonstrate that controlled release is achieved with membrane weights ranging from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

TABLE 4A

Standard Parameters for Sustained-Release Coating in Caleva Mini-Coater/Drier 2	
Parameter	Setting
Batch size	3-12 Tablets
Inlet temperature	40° C.
Air flow setting	70-85%
Solution flow rate	18 ml/hr
Agitator setting	32
Atomization pressure	0.5 bar
Gun position	Adjusted to achieve desired deposition

Example 5—Effect of Membrane Weight with Hydroxypropyl Cellulose as Pore Former in Functional Coating

Following procedures of Example 4, 12 tablets from Example 1 were coated with a film consisting of 36.5% HPC-EF, 5.0% dibutyl sebacate (DBS), and 58.5% EC-10 (all percentages by weight) coated from a solution consisting of 7% solids in 95/5 alcohol/water. The results shown in FIG. 4 demonstrate that controlled release over a relevant

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time period is achieved with membrane weights ranging from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

Example 6—Effect of Poloxamer Level in Functional Coating

In addition to adjustment of membrane weight, another useful means of controlling release rate or duration is by adjustment of the pore-former content of the formulation. Following procedures of Example 4, two additional solutions consisting of (a) 25% P188 by weight/75% EC-10 by weight and (b) 40% P188 by weight/60% EC-10 by weight were prepared as 7% (w/w) solutions in 95/5 alcohol/water. In each of the two separate coatings, four tablets from Example 1 were coated to 41 mg. The dissolution profiles are shown in FIG. 5, along with that of the 40 mg set of Example 4 for comparison. The results demonstrate that poloxamer level can be adjusted at least over the range of 25%-40% by weight, while still providing controlled release of the drug.

Example 7—Effect of Hydroxypropyl Cellulose Level in Functional Coating

In a fashion similar to Example 6, the effect of HPC level in the functional coating was evaluated over the range of 30%-50% by weight. Three separate coating solutions were prepared with 30%, 40%, and 50% HPC-EF; 5% DBS; and the balance EC-10. All solutions were prepared with 7% total components in 95/5 alcohol/water. In each coating, 4 tablets from Example 1 were coated to 40-41 mg/tablet weight gain. The dissolution profiles shown in FIG. 6 demonstrate controlled release of the drug was achieved with HPC levels of at least 30-50% by weight.

Example 8—Effect of Hydroxypropyl Cellulose Molecular Weight when Used in Functional Coating

Hydroxypropyl cellulose is supplied in several molecular weight grades, many of which may be suitable for use as pore-formers in ethylcellulose films. Two such grades (Klucel "EF" and "JF", supplied by Ashland) corresponding to 80,000 daltons and 140,000 daltons were evaluated with other components fixed. Following procedures of Example 4, solutions were prepared with 40% HPC, 5% DBS, and 55% EC-10 (all percentages by weight) using 7% total components in 95/5 alcohol/water. In each coating, 4 tablets from Example 1 were coated to 40-41 mg/tablet weight gain. The results shown in FIG. 7 demonstrate a modest effect of molecular weight and that the two grades tested provide for acceptable release profiles.

Example 9—Effect of Ethylcellulose Molecular Weight or Viscosity

Another consideration is the molecular weight, or viscosity, of ethylcellulose. Two grades were evaluated, corresponding to 4 cPs and 10 cPs viscosity for a 5% solution. Following procedures of Example 4, two solutions were prepared corresponding to 58.5 wt % ethylcellulose (EC-4 or EC-10), 36.5 wt % HPC-EF, and 5.0 wt % DBS having 7% w/w total components in 95/5 alcohol/water. Tablets from Example 1 were coated to 40 mg/tablet weight gain, and dissolution profiles are shown as FIG. 8. The results indicate both grades of ethylcellulose provide for acceptable

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profiles, and suggest that other ethylcellulose grades (such as 20 cPs) may also be acceptable.

Example 10—Demonstration of Alcohol Ruggedness of Controlled Release Sodium Oxybate Tablets

Co-administration of sustained-release dosage forms with alcoholic beverages is a relevant concern, as ethanol is known to dissolve certain rate-controlling components that would not otherwise be dissolved. In some dosage forms, this may lead to dose-dumping. As ethanol is rapidly absorbed in the stomach, a relevant test involves dissolution of the dosage form in vodka (40% ethanol nominal) for 2 hours (representing gastric retention time), followed by normal dissolution in de-ionized water.

This test was performed on sustained-release tablets from Example 9 (36.5 wt % HPC EF, 5 wt % DBS, 58.5 wt % EC-4). The analysis of sodium oxybate by conductivity was corrected for the different response in vodka vs. de-ionized water. The results shown in FIG. 9A indicate that dissolution is slower in Vodka, and that no dose-dumping occurred.

Likewise, a similar test was performed on sustained-release tablets with a film comprised of 33 wt % P188 and 67 wt % EC-10. Those results, shown in FIG. 9B, also indicate slower release in vodka and no dose-dumping.

Example 11—Aqueous Coating of Controlled Release Film

Due to the hygroscopic nature of sodium oxybate, coating the rate-controlling film from an alcoholic solution is desirable. However, use of ethylcellulose aqueous dispersions is attractive for environmental and cost considerations. A film consisting of 30 wt % HPC EF and 70 wt % Surelease (aqueous ethylcellulose dispersion) was deposited on tablets from Example 1 as follows. First, 1.37 grams of HPC EF was dissolved in 22.6 grams de-ionized water. This was then poured into 32.5 grams of Surelease E-7-19040-clear while stirring. Eight tablets were coated in the Caleva Mini-coater/Drier 2 with flow rate of 15 ml/hr and 58° C. inlet temperature. Samples removed at 24 mg and 40 mg were then tested for dissolution, with no post-coating heat treatment. The results are shown in FIG. 10.

Example 12—Calcium Oxybate Controlled Release

A controlled release dosage form for delivery of calcium oxybate was prepared by generally following procedures of Example 1 found in U.S. Pat. No. 4,393,296 (Klosa, Production of Nonhygroscopic Salts of 4-Hydroxybutyric Acid). The isolated calcium oxybate was milled to pass through a 16-mesh screen. For this study, a small sample comprising 9.3 grams of calcium oxybate was blended with 0.19 grams of sodium stearyl fumarate (Pruv, JRS Pharma, Rosenberg, Germany). 800 mg aliquots of this 98% calcium oxybate and 2% sodium stearyl fumarate were then directly compressed into tablets using 0.325"x0.705" modified oval tooling and a Carver press with 1-ton applied force. Following procedures of Example 4, nine tablets were coated with a film having 33% poloxamer 188 and 67% EC-10 from a solution of 7% w/w solids in 95/5 alcohol/water. Two tablets were removed at each intermediate coating weight corresponding to 20 mg, 32 mg, 41 mg, and finally at 60 mg. The dissolution profiles are shown as FIG. 11. These results

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using calcium oxybate follow the general behavior of sodium oxybate demonstrated in Example 4.

Example 13—Clinical Evaluation of Controlled Release Dosage Forms

An open-ended, randomized, crossover study was conducted to evaluate controlled release dosage forms as described herein. The controlled release dosage forms were formulated to deliver sodium oxybate and were compared to a sodium oxybate oral solution (commercially available as Xyrem® (sodium oxybate) oral solution). The study was conducted in healthy male and female volunteers.

Four different sodium oxybate formulations were administered to patients. The first, designated herein as Treatment A, was the sodium oxybate oral solution containing 375 mg/ml sodium oxybate. Treatments B through E, as designated herein, involved administration of three controlled release dosage forms (Treatments B through D), with one of the controlled release dosage forms being used to administer two different doses of sodium oxybate (Treatments D and E). The controlled release dosage forms administered as Treatment B included 750 mg sodium oxybate per dosage form and were produced with a CR core and functional overcoat as described in Example 1 and Example 2, the controlled release dosage forms administered as Treatment C included 750 mg sodium oxybate per dosage form and were produced

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as described in Example 1 and Example 4, and the controlled release dosage forms administered as Treatments D and E included 1,000 mg sodium oxybate per dosage form and were produced with a CR core (750 mg sodium oxybate), functional overcoat, and IR overcoat (250 mg sodium oxybate) as described in Examples 1 through 3.

Patients were divided into two groups. The first group received Treatment A, Treatment B, and Treatment C over the course of the clinical study, with a washout period between each treatment. Treatment A was administered to each patient as two 3 g doses given four hours apart (one dose at time zero and the second dose four hours later), for a total dose of 6 g sodium oxybate. Treatments B and C were administered to each patient only at time zero, with each treatment being administered as 8 tablets, providing a total dose of 6 g sodium oxybate. Blood samples from each patient were taken at various intervals and analyzed by LC/MS for total sodium oxybate content in the plasma. A total of 29 patients received Treatment A, a total of 19 patients received Treatment B, and a total of 19 patients received Treatment C. The mean plasma concentration of sodium oxybate over time achieved by each of the treatments is shown in FIG. 12 (Treatment A and Treatment B) and FIG. 13 (Treatment A and Treatment C), and a summary of pharmacokinetic parameters provided by Treatments A through C are provided in Table 5.

TABLE 5

Summary of PK Parameters for Treatments A, B, C						
	λ_z (1/hr)	$T_{1/2}$ (hr)	T_{max} (hr) ^a	C_{max} (ug/ml)	AUC_{last} (hr * ug/ml)	AUC_{inf} (hr * ug/ml)
Treatment A						
N	29	29	29	29	29	29
Mean	1.22	0.60	4.50 (0.5, 4.75)	130.79	350.84	351.20
SD	0.27	0.13		31.52	116.74	116.74
CV %	21.93	22.61		24.10	33.27	33.24
Mean	1.19	0.58		127.37	333.33	333.72
Treatment B						
N	18	18	19	19	19	18
Mean	0.62	1.22	2.00 (1.50, 5.00)	41.78	188.23	196.25
SD	0.16	0.40		18.40	103.60	102.50
CV %	26.44	32.58		44.03	55.04	52.23
Mean	0.59	1.17		38.46	163.80	173.33
Treatment C						
N	19	19	19	19	19	19
Mean	0.74	0.99	2.50 (1.00, 5.00)	50.49	221.64	222.60
SD	0.16	0.23		15.83	106.85	106.80
CV %	22.25	22.93		31.35	48.21	47.98
Mean	0.72	0.96		48.10	200.08	201.12

The second group was administered Treatment A, Treatment D, and Treatment E during over the course of the clinical study, with a washout period between each treatment. Again, Treatment A was administered to each patient as two 3 g doses given four hours apart (one dose at time zero and the second dose four hours later), for a total dose of 6 g sodium oxybate. Treatments D and E were administered to each patient only at time zero. Patients receiving Treatment D were administered 4 tablets at time zero, providing a total dose of 4 g sodium oxybate, and patients receiving Treatment E were administered 8 tablets at time zero, providing a total dose of 8 g sodium oxybate. Blood samples from each patient were taken at various intervals and analyzed by LC/MS for total sodium oxybate content in the plasma. A total of 30 patients received Treatment A, and a total of 30 patients received Treatments D and E. The mean plasma concentration of sodium oxybate over time achieved by each of the treatments is shown in FIG. 14, and a summary of pharmacokinetic parameters provided by Treatments A through C are provided in Table 6.

TABLE 6

Summary of PK Parameters for Treatments A, D, E						
	λ_{z1} (1/hr)	$T_{1/2}$ (hr)	T_{max} (hr) ^a	C_{max} (ug/ml)	AUC_{clast} (hr * ug/ml)	AUC_{inf} (hr * ug/ml)
Treatment A						
N	30	30	30	30	30	30
Mean	1.08	0.71	4.50 (0.50, 5.50)	114.59	301.28	301.59
SD	0.31	0.27		27.91	100.85	100.87
CV %	29.00	37.90		24.36	33.47	33.45
Mean	1.03	0.67		111.20	285.47	285.79
Treatment D						
N	30	30	30	30	30	30
Mean	0.46	1.63	0.75 (0.50, 2.50)	25.10	64.44	65.58
SD	0.14	0.47		7.33	20.36	20.26
CV %	30.27	29.00		29.20	31.60	30.90
Mean	0.44	1.56		24.01	61.31	62.55
Treatment E						
N	30	30	30	30	30	30
Mean	0.59	1.36	1.00 (0.50, 5.00)	59.52	242.30	243.80
SD	0.20	0.64		17.72	117.15	116.79
CV %	34.57	46.91		29.77	48.35	47.91
Mean	0.55	1.25		56.89	216.33	218.12

^a T_{max} is summarized as median (min, max).

It will be obvious to those having skill in the art that many changes may be made to the details of the above-described embodiments without departing from the underlying principles of the invention. The scope of the present invention should, therefore, be determined only by the following claims.

The invention claimed is:

1. A method for treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof comprising delivering to the patient a formulation comprising a sustained release portion comprising about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, wherein: the sustained release portion comprises a functional coating and a core, the functional coating is deposited over the core; the core comprises at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate;

the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

2. The method of claim 1, wherein the sustained release portion releases about 60% to about 90% of its gamma-hydroxybutyrate by about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

3. The method of claim 1, wherein the sustained release portion releases about 10% or less of its gamma-hydroxybutyrate by about 1 hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

4. The method of claim 1, wherein the sustained release portion comprises hydrogenated vegetable oil, hydrogenated castor oil, or mixtures thereof.

5. The method of claim 1, wherein the sustained release portion comprises a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.

6. The method of claim 5, wherein the sustained release portion comprises a sodium salt of gamma-hydroxybutyrate.

7. The method of claim 1, wherein the one or more methacrylic acid-methyl methacrylate co-polymers comprise from about 30% to about 45% by weight of the functional coating.

8. The method of claim 1, wherein the formulation further comprises an immediate release portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate.

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9. The method of claim 8, wherein the immediate release portion comprises a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.

10. The method of claim 9, wherein the immediate release portion comprises a sodium salt of gamma-hydroxybutyrate.

11. The method of claim 8, wherein the immediate release portion is a dry powder formulation, an immediate release tablet, an encapsulated formulation, a liquid solution, or liquid suspension.

12. The method of claim 8, wherein the immediate release portion comprises about 55 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate.

13. The method of claim 8, wherein the formulation releases at least about 30% of its gamma-hydroxybutyrate

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by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm; and greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.




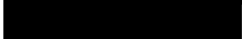

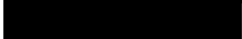
14. The method of claim 13, wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 7 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

15. The method of claim 13, wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

* * * * *

EXHIBIT 3

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

<hr/>		
JAZZ PHARMACEUTICALS, INC.,)	
)	
Plaintiff,)	
)	
v.)	C.A. No. 21-691 (MN)
)	
AVADEL CNS PHARMACEUTICALS LLC,)	
)	
Defendant.)	
<hr/>		
JAZZ PHARMACEUTICALS, INC. and)	
JAZZ PHARMACEUTICALS IRELAND)	
LIMITED,)	
)	
Plaintiffs,)	
)	C.A. No. 21-1138 (MN)
v.)	
)	
AVADEL CNS PHARMACEUTICALS LLC,)	
)	
Defendant.)	
<hr/>		
JAZZ PHARMACEUTICALS, INC. and)	
JAZZ PHARMACEUTICALS IRELAND)	
LIMITED,)	
)	
Plaintiffs,)	
)	C.A. No. 21-1594 (MN)
v.)	
)	
AVADEL CNS PHARMACEUTICALS LLC,)	
)	
Defendant.)	
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PLAINTIFFS' FINAL INFRINGEMENT CONTENTIONS

'956 Patent	Avadel's NDA Product
<p>1. A method for treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof</p>	<p>The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.</p> <p>The administration of Avadel's NDA Product will treat cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof. <i>See</i> AVDL_00045593; AVDL_00045600; AVDL_00045606; AVDL_00045610; AVDL_00052477-78; AVDL_00052493; AVDL_01270890-911.</p> <p>Avadel's proposed package insert for its NDA Product instructs and encourages the administration of Avadel's NDA Product for the treatment of cataplexy or excessive daytime sleepiness associated with narcolepsy in patients. <i>See</i> AVDL_00052477-502; AVDL_01270890-911; AVDL_00045591-5611.</p> <p>Specifically, Avadel's proposed package insert as well as its NDA states the proposed indication for the use of its NDA Product is "cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy." AVDL_00045593; AVDL_00045600; AVDL_00045606; AVDL_00045610; AVDL_00052477-78; AVDL_00052493; AVDL_01270890-91.</p> <p>Avadel's investigator's brochure for its NDA Product also instructs and encourages the administration of Avadel's NDA Product for the treatment of cataplexy or excessive daytime sleepiness associated with narcolepsy in patients. <i>See</i> AVDL_00046937; AVDL_00046980; AVDL_00090505-573.</p>
<p>comprising delivering to the patient a formulation comprising immediate release and sustained release portions, each portion comprising at least one pharmaceutically active ingredient</p>	<p>The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.</p>

'931 Patent	Avadel's NDA Product
<p>1. A method for treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof</p>	<p>The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.</p> <p>The administration of Avadel's NDA Product will treat cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof. <i>See</i> AVDL_00045593; AVDL_00045600; AVDL_00045606; AVDL_00045610; AVDL_00052477-78; AVDL_00052493; AVDL_01270890-91.</p> <p>Avadel's proposed package insert for its NDA Product instructs and encourages the administration of Avadel's NDA Product for the treatment of cataplexy or excessive daytime sleepiness associated with narcolepsy in patients. <i>See</i> AVDL_00052477-502; AVDL_00045591-5611; AVDL_01270890-911. Specifically, Avadel's proposed package insert as well as its NDA states the proposed indication for the use of its NDA Product is "cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy." AVDL_00045593; AVDL_00045600; AVDL_00045606; AVDL_00045610; AVDL_00052477-78; AVDL_00052493; AVDL_01270890-91.</p> <p>Avadel's investigator's brochure for its NDA Product also instructs and encourages the administration of Avadel's NDA Product for the treatment of cataplexy or excessive daytime sleepiness associated with narcolepsy in patients. <i>See</i> AVDL_00046937; AVDL_00046980; AVDL_00090505-573.</p>
<p>comprising delivering to the patient a formulation comprising a sustained release portion comprising about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from</p>	<p>The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.</p> <p>Avadel's proposed package insert for its NDA Product instructs and encourages delivering Avadel's NDA Product to patients. <i>See</i> AVDL_00052477-502; AVDL_01270890-911.</p>

provides for more “physiologically relevant dissolution parameters . . . than the [two] single media methods.” *Id.* A POSA would not measure controlled release by using a method that was not physiologically meaningful. Instead, by evaluating data derived from a method that provides for more “physiologically relevant dissolution parameters . . . than the single media methods,” it is clear that the controlled release portion of Avadel’s NDA Product releases over a period of at least about 2 to about 8 hours. *See* AVDL_00051157-69; AVDL_00051054-76. Thus, Avadel infringes this claim element.

B. Avadel’s NDA Product Will Infringe Each Asserted Claim of the ’079 Patent

As set forth in the chart below, each element of each asserted claim will be met by Avadel’s FT218 product.

'079 Patent	Avadel’s NDA Product
1. A method of treating narcolepsy in a patient in need thereof, the method comprising:	<p>The use of Avadel’s NDA Product will literally meet this limitation. This is supported by Avadel’s document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.</p> <p>The administration of Avadel’s NDA Product will treat narcolepsy in a patient in need thereof. <i>See</i> AVDL_00045593; AVDL_00045600; AVDL_00045606; AVDL_00045610; AVDL_00052477-78; AVDL_00052493; AVDL_00102530-32; AVDL_00102548-49; AVDL_01270890-91.</p> <p>Avadel’s proposed package insert for its NDA Product instructs and encourages the administration of Avadel’s NDA Product for the treatment of narcolepsy in patients. <i>See</i> AVDL_00052477-502; AVDL_00045591-5611; AVDL_00102530-552; AVDL_01270890-911.</p> <p>Specifically, Avadel’s proposed package insert as well as its NDA states the proposed indication for the use of its NDA Product is “cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.” AVDL_00045593; AVDL_00045600; AVDL_00045606; AVDL_00045610; AVDL_00052477-78; AVDL_00052493; AVDL_00102530-32; AVDL_00102548-49; AVDL_01270890-91.</p>

'079 Patent	Avadel's NDA Product
<p>wherein the administering promotes the patient to sleep for 6 to 8 hours.</p>	<p>The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.</p> <p>The use of Avadel's NDA Product will promote the patient to sleep for 6 to 8 hours. <i>See</i> AVDL_00090505-573; AVDL_00045591-611; AVDL_00046655-746; AVDL_00086258-365; AVDL_00087616-754; AVDL_00088590-886.</p> <p>Avadel's investigator's brochure states that its NDA Product will "allow[] patients at least six hours of continuous and improved sleep." AVDL_00090528. It further states that "plasma GHB concentration maintained throughout the night, as well as gradual decline to lowest levels by 8-10 hours after dosing." AVDL_00090514; <i>see also</i> AVDL_00012430; AVDL_00046951; AVDL_00049203; AVDL_00045598; AVDL_00046686-93; AVDL_00086281; AVDL_00087632.; AVDL_00088595; AVDL_00088645-46.</p>
<p>6. The method of claim 1,</p>	<p><i>See</i> claim 1.</p>
<p>wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, or 70 mEq of oxybate.</p>	<p>The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.</p> <p>The amount of oxybate administered to a patient by the use of Avadel's NDA Product is 35 mEq, 45 mEq, or 70 mEq of oxybate. AVDL_00102530-33; AVDL_00052477-79; AVDL_01270890-92.</p> <p>According to Avadel's proposed package insert, Avadel's NDA Product will be administered at doses of 4.5 g, 6 g, 7.5 g, and 9 g oxybate. AVDL_00102530-33; AVDL_00052477-79; AVDL_01270890-92.</p> <p>A 4.5 g dose of sodium oxybate is 35.7 mEq oxybate. '079 Patent at 20:17-18. As the relationship between grams and milliequivalents are proportional, this means that: 6 g dose of</p>

'079 Patent	Avadel's NDA Product
9. The method of claim 1,	<i>See</i> claim 1.
wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.	<p>The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.</p> <p>Avadel's NDA Product further comprises malic acid. <i>See</i> AVDL_00045655-668; AVDL_00044220-260; AVDL_00045669-671; AVDL_00102530-552.</p> <p>Avadel's NDA states that its NDA Product contains malic acid. AVDL_00045661-62; AVDL_00045670; AVDL_00044237-38; AVDL_00102545.</p>
10. A method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof, the method comprising:	<p>The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.</p> <p>The administration of Avadel's NDA Product will treat cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof. <i>See</i> AVDL_00045593; AVDL_00045600; AVDL_00045606; AVDL_00045610; AVDL_00052477-78; AVDL_00052493; AVDL_00102530-32; AVDL_00102548-49; AVDL_01270890-91.</p> <p>Avadel's proposed package insert for its NDA Product instructs and encourages the administration of Avadel's NDA Product for the treatment of cataplexy or excessive daytime sleepiness associated with narcolepsy in patients. <i>See</i> AVDL_00052477-502; AVDL_00045591-5611; AVDL_00102530-552; AVDL_01270890-911. Specifically, Avadel's proposed package insert as well as its NDA states the proposed indication for the use of its NDA Product is "cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy." AVDL_00045593; AVDL_00045600; AVDL_00045606; AVDL_00045610;</p>

'079 Patent	Avadel's NDA Product
	suspension of the oxybate formulation in Avadel's NDA Product is to be mixed with water immediately prior to administration at bedtime.
14. The method of claim 10,	<i>See claim 10.</i>
wherein the administering promotes the patient to sleep for 6 to 8 hours.	<p>The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.</p> <p>The use of Avadel's NDA Product will promote the patient to sleep for 6 to 8 hours. <i>See</i> AVDL_00090505-573; AVDL_00045591-611; AVDL_00046655-746; AVDL_00086258-365; AVDL_00087616-754; AVDL_00088590-886.</p> <p>Avadel's investigator's brochure states that its NDA Product will "allow[] patients at least six hours of continuous and improved sleep." AVDL_00090528. It further states that "plasma GHB concentration maintained throughout the night, as well as gradual decline to lowest levels by 8-10 hours after dosing." AVDL_00090514; <i>see also</i> AVDL_00012430; AVDL_00046951; AVDL_00049203; AVDL_00045598; AVDL_00046686-93; AVDL_00086281; AVDL_00087632.; AVDL_00088595; AVDL_00088645-46.</p>
15. The method of claim 10,	<i>See claim 10.</i>
wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.	The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.

EXHIBIT 4



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

128521 7590 12/18/2020
 Cooley LLP / Jazz Pharmaceuticals
 1299 Pennsylvania Ave., NW, Suite 700
 Washington, DC 20004

EXAMINER

GOTFREDSON, GAREN

ART UNIT

PAPER NUMBER

1619

DATE MAILED: 12/18/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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17/012.823

09/04/2020

Clark ALLPHIN

JAZZ-043/06US

1073

306882-2458

TITLE OF INVENTION: CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	03/18/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

128521 7590 12/18/2020
Cooley LLP / Jazz Pharmaceuticals
1299 Pennsylvania Ave., NW, Suite 700
Washington, DC 20004

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

17/012,823	09/04/2020	Clark ALLPHIN	JAZZ-043/06US 306882-2458	1073
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TITLE OF INVENTION: CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	03/18/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
GOTFREDSON, GAREN	1619	424-495000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

1 _____

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☐ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/012,823	09/04/2020	Clark ALLPHIN	JAZZ-043/06US 306882-2458	1073
128521	7590	12/18/2020	EXAMINER	
Cooley LLP / Jazz Pharmaceuticals 1299 Pennsylvania Ave., NW, Suite 700 Washington, DC 20004			GOTFREDSON, GAREN	
			ART UNIT	PAPER NUMBER
			1619	
DATE MAILED: 12/18/2020				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
 (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.** Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b) (2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 17/012,823	Applicant(s) ALLPHIN et al.	
	Examiner GAREN GOTFREDSON	Art Unit 1619	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to papers submitted 12/4/20 and 12/11/20.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are 109-135. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: ____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date ____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. <input type="checkbox"/> Notice of References Cited (PTO-892)	5. <input type="checkbox"/> Examiner's Amendment/Comment
2. <input checked="" type="checkbox"/> Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date ____.	6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance
3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material ____.	7. <input type="checkbox"/> Other ____.
4. <input type="checkbox"/> Interview Summary (PTO-413), Paper No./Mail Date ____.	

/Patricia Duffy/ Primary Examiner, Art Unit 1645	
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Application/Control Number: 17/012,823
Art Unit: 1619

Page 2

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 9/16/20 was filed prior to the mailing date of a first Action on the merits. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, it was considered by the Examiner.

Statement of Reasons for Allowance

Conte (US Pat. No. 5,594,030; of record in IDS) discloses the treatment of an alcohol addiction by administering a controlled release solid dosage formulation comprising a sustained release core comprising GHB and optionally a functional copolymer coating over the core comprising methacrylic acid ester, methyl methacrylate, and ethyl acrylate (Summary of the Invention at column 3; column 4, 8th full paragraph through column 5, 1st paragraph; Examples 1 and 2).

The prior art does not teach or suggest, however, a method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy by administering a sustained release formulation as claimed, wherein the composition comprises a methacrylic acid-methyl methacrylate copolymer as recited by the claims. The claimed copolymer coating, unlike the Conte polymer, is water soluble only at or above a certain pH, such that the Conte polymer will possess a different release profile as discussed in Applicant's remarks submitted on June 8, 2020 in U.S. Pat. Appl. No. 16/025,487, and

Application/Control Number: 17/012,823
Art Unit: 1619

Page 3

that will not result in a composition having the release profile that Applicant determined was desirable after conducting modeling and absorption studies as discussed in the affidavit submitted on April 20, 2020 in U.S. Pat. Appl. No. 16/025,487.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GAREN GOTFREDSON whose telephone number is (571)270-3468. The examiner can normally be reached on M-F 9AM-6PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Blanchard can be reached on 5712720827. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <https://ppair-my.uspto.gov/pair/PrivatePair>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access

Application/Control Number: 17/012,823

Page 4

Art Unit: 1619

to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GAREN GOTFREDSON/
Examiner, Art Unit 1619

/Patricia Duffy/
Primary Examiner, Art Unit 1645

EXHIBIT 5



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

128521 7590 01/06/2021
 Cooley LLP / Jazz Pharmaceuticals
 1299 Pennsylvania Ave., NW, Suite 700
 Washington, DC 20004

EXAMINER

GOTFREDSON, GAREN

ART UNIT

PAPER NUMBER

1619

DATE MAILED: 01/06/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/012,831	09/04/2020	Clark ALLPHIN	JAZZ-043/05US 306882-2457	2799

TITLE OF INVENTION: CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	04/06/2021

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

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If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

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III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

128521 7590 01/06/2021
Cooley LLP / Jazz Pharmaceuticals
1299 Pennsylvania Ave., NW, Suite 700
Washington, DC 20004

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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17/012,831 09/04/2020 Clark ALLPHIN JAZZ-043/05US 2799
306882-2457

TITLE OF INVENTION: CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	04/06/2021

EXAMINER	ART UNIT	CLASS-SUBCLASS
GOTFREDSON, GAREN	1619	424-495000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☐ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/012,831	09/04/2020	Clark ALLPHIN	JAZZ-043/05US 306882-2457	2799
128521	7590	01/06/2021	EXAMINER	
Cooley LLP / Jazz Pharmaceuticals 1299 Pennsylvania Ave., NW, Suite 700 Washington, DC 20004			GOTFREDSON, GAREN	
			ART UNIT	PAPER NUMBER
			1619	

DATE MAILED: 01/06/2021

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
 (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.** Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b) (2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 17/012,831	Applicant(s) ALLPHIN et al.	
	Examiner GAREN GOTFREDSON	Art Unit 1619	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to papers submitted 9/4/20.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are 109-123. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. <input type="checkbox"/> Notice of References Cited (PTO-892)	5. <input type="checkbox"/> Examiner's Amendment/Comment
2. <input checked="" type="checkbox"/> Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.	6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance
3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.	7. <input type="checkbox"/> Other _____.
4. <input type="checkbox"/> Interview Summary (PTO-413), Paper No./Mail Date _____.	

/Patricia Duffy/ Primary Examiner, Art Unit 1645	
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DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 9/16/20 was filed prior to the mailing date of a first Action on the merits. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, it was considered by the Examiner.

Statement of Reasons for Allowance

Conte (US Pat. No. 5,594,030; of record in IDS) discloses the treatment of an alcohol addiction by administering a controlled release solid dosage formulation comprising a sustained release core comprising GHB and optionally a functional copolymer coating over the core comprising methacrylic acid ester, methyl methacrylate, and ethyl acrylate (Summary of the Invention at column 3; column 4, 8th full paragraph through column 5, 1st paragraph; Examples 1 and 2).

The prior art does not teach or suggest, however, a method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy by administering a sustained release formulation as claimed, wherein the composition comprises a methacrylic acid-methyl methacrylate copolymer as recited by the claims. The claimed copolymer coating, unlike the Conte polymer, is water soluble only at or above a certain pH, such that the Conte polymer will possess a different release profile as discussed in

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Applicant's remarks submitted on June 8, 2020 in U.S. Pat. Appl. No. 16/025,487, and that will not result in a composition having the release profile that Applicant determined was desirable after conducting modeling and absorption studies as discussed in the affidavit submitted on April 20, 2020 in U.S. Pat. Appl. No. 16/025,487.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GAREN GOTFREDSON whose telephone number is (571)270-3468. The examiner can normally be reached on M-F 9AM-6PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Blanchard can be reached on 5712720827. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <https://ppair-my.uspto.gov/pair/PrivatePair>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access

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to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GAREN GOTFREDSON/
Examiner, Art Unit 1619

/Patricia Duffy/
Primary Examiner, Art Unit 1645

EXHIBIT 6



US011077079B1

(12) **United States Patent**
Allphin et al.

(10) **Patent No.:** **US 11,077,079 B1**

(45) **Date of Patent:** **Aug. 3, 2021**

- (54) **GHB FORMULATION AND METHOD FOR ITS MANUFACTURE**
- (71) Applicant: **JAZZ PHARMACEUTICALS IRELAND LIMITED**, Dublin (IE)
- (72) Inventors: **Clark Allphin**, Seattle, WA (US); **Scott Bura**, Gilroy, CA (US)
- (73) Assignee: **Jazz Pharmaceuticals Ireland Limited**, Dublin (IE)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
- (21) Appl. No.: **17/118,041**
- (22) Filed: **Dec. 10, 2020**

Related U.S. Application Data

- (63) Continuation of application No. 16/448,598, filed on Jun. 21, 2019, now abandoned, which is a continuation of application No. 15/047,586, filed on Feb. 18, 2016, now Pat. No. 10,398,662.
- (60) Provisional application No. 62/117,889, filed on Feb. 18, 2015.
- (51) **Int. Cl.**
A01N 25/04 (2006.01)
A61K 31/19 (2006.01)
A61K 31/785 (2006.01)
A61K 38/02 (2006.01)
A61K 9/50 (2006.01)
- (52) **U.S. Cl.**
CPC **A61K 31/19** (2013.01); **A61K 9/5031** (2013.01); **A61K 31/785** (2013.01); **A61K 38/02** (2013.01)
- (58) **Field of Classification Search**
CPC **A61K 31/19**; **A61K 31/785**; **A61K 9/5031**; **A61K 38/02**
USPC 424/497
See application file for complete search history.

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(Continued)

Primary Examiner — Yanzhi Zhang

(74) Attorney, Agent, or Firm — Cooley LLP

(57) **ABSTRACT**

The present application relates to GHB formulations and methods for manufacturing the same.

18 Claims, No Drawings

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GHB FORMULATION AND METHOD FOR ITS MANUFACTURE**CROSS REFERENCE TO RELATED APPLICATION**

This application is a continuation of U.S. application Ser. No. 16/448,598, filed Jun. 21, 2019, which is a continuation of U.S. application Ser. No. 15/047,586, filed Feb. 18, 2016, now U.S. Pat. No. 10,398,662, which claims priority to U.S. Provisional Application Ser. No. 62/117,889, filed Feb. 18, 2015, the disclosures of which are herein incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

Gamma-hydroxybutyrate (GHB), also known as "oxybate," is an endogenous compound with hypnotic properties that is found in many human body tissues. GHB is present, for example, in the mammalian brain and other tissues. In the brain, the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (See Snead and Morley, 1981, Brain Res. 227(4): 579-89). The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e., daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency, reduces sleep apnea, and improves general anesthesia (see, e.g., U.S. Pat. Nos. 6,472,431; 6,780,889; 7,262,219; 7,851,506; 8,263,650; and 8,324,275; each of which is incorporated herein by reference in its entirety).

Sodium oxybate (Na.GHB), commercially sold as Xyrem®, is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. It can be used for other sleep time disturbances. Na.GHB has also been reported to be effective for relieving pain and improving function in patients with fibromyalgia syndrome (See Scharf et al., 2003, J. Rheumatol. 30: 1070; Russell et al., 2009, Arthritis. Rheum. 60: 299), and in alleviating excessive daytime sleepiness and fatigue in patients with Parkinson's disease, improving myoclonus and essential tremor, and reducing tardive dyskinesia and bipolar disorder (See Ondo et al., 2008, Arch. Neural. 65: 1337; Frucht et al., 2005, Neurology 65: 1967; Berner, 2008, J. Clin. Psychiatry 69: 862).

SUMMARY OF THE INVENTION

GHB has a short in vivo half-life, so various embodiments of the invention include a formulation and a method for manufacturing a GHB formulation. One embodiment of the invention is a GHB formulation comprising polymeric beads and pharmaceuticals acceptable excipients. The formulation can be a solid or a liquid. Additional agents, such as surfactants, may be added to control the release of GHB from within the polymeric bead, such as sodium lauryl sulfate or stearic acid. The beads can be coated with a flexible film. Optionally, the formulation can contain supplemental anions separate from the coated or uncoated resin particles to facilitate exchange of the GHB when natural (e.g., physiologically produced) anions in the gut are depleted.

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In another embodiment of the invention, a precursor to GHB, called gamma butyrolactone (GBL) is loaded onto a hydroxide form Type 1 strong base anion resin (or its equivalent) and the GBL is converted to GHB in the bead to form a GHB resinate product. One can achieve high loading efficiency of the GHB resinate product and a high reaction rate on the resin. Furthermore, organic non-anionic byproducts made in reaction or present in the GBL would not be captured on the resin.

In another embodiment of the invention, one can fully load GHB on the resin, then load a lipophilic agent on the resin with higher selectivity for the resin than GHB. The agent will slow the release of GHB.

In another embodiment, one can fully load an anionic hydrophobic agent, such as stearic acid, onto the resin with lower selectivity for the resin than GHB and then subsequently load GHB less completely, thereby retaining much of the hydrophobic agent and promoting a slower release of GHB.

In still another embodiment of the invention, the hydroxide-bearing resin beads are coated with a flexible film, then loaded with GBL which, in turn, will diffuse through the film and react with the hydroxyl anions of the resin and form the GHB resinate in-situ. The coating will provide further controlled release characteristics. Examples of such coatings include films comprising polyvinyl acetate (PVAcetate), Eudragit RS, ethylcellulose, cellulose acetate or an enteric coating such as acrylic acid-based Eudragit L100, FS100 or L55, cellulose acetate phthalate, and shellac. It is understood that these films can be modified with pore formers to adjust permeability or degree of enteric protection. The coating may also be combined with suitable plasticizer and anti-tack agents to facilitate coating. Finely ground resin beads may also be encapsulated within polysaccharide gel structures that confer enteric protection, through ionotropic gelation as with calcium alginate encapsulation.

Other embodiments include reducing the amount of water in the formulation. Oral administration may be achieved while reducing the amount of water by using agents that increase flow, such as slippants to reduce viscosity. Example slippants include polyethylene oxide (PEG) (and its equivalents) which is available in various grades of varying molecular weight and molecular weight distribution.

DETAILED DESCRIPTION OF THE INVENTION

One embodiment of the invention is a GHB formulation comprising polymeric beads and pharmaceuticals acceptable excipients. The formulation can be in the form of a solid or a liquid. Additional agents, such as surfactants, may be added to control the release of GHB from within the polymeric bead, such as sodium lauryl sulfate or stearic acid. The beads can be coated with a flexible film. Background information on GHB and its related compounds, use and methods for manufacture are listed below. Also, background information on ion exchange resins, their manufacture and uses can be found in the references listed below. The new formulations of the present invention described herein provide favourable sustained release profiles for GHB.

The following U.S. patents and applications relate to GHB and are hereby incorporated by reference in their entireties for all purposes: U.S. Pat. Nos. 6,472,431, 8,263,650, 8,324,275; 8,859,619; 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 8,461,197; 8,591,922; 8,731,963; 8,759,394; 8,771,735; 8,772,306; 8,778,301; 8,778,398; 8,901,173; and 2012/0076865. The following patents

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are also incorporated by reference: U.S. Pat. Nos. 5,380,937; 4,393,236 German Patent DD 237,309 A1; and British Pat. No. 922,029.

Information on ion exchange resins, their manufacture and uses can be found in the following references which are hereby incorporated by reference in their entireties for all purposes. Mahore J. G, Wadher K. J, Umekar M. J, Bhoyar P. K., Ion Exchange Resins: Pharmaceutical Applications And Recent Advancement, International Journal of Pharmaceutical Sciences Review and Research, Volume 1, Issue 2, March-April 2010; Article 002; Munot, Neha M., et al. "Ion exchange resins in pharmaceuticals: A review." Journal of Pharmacy Research 3.12 (2010). Singh, Inderbir, et al. "Ion exchange resins: drug delivery and therapeutic applications." FABAD J. Pharm. Sci 32 (2007): 91-100; Srikanth, M. V., et al. "Ion-exchange resins as controlled drug delivery carriers." Journal of Scientific Research 2.3 (2010): 597; Singh, Inderbir, et al. "Ion exchange resins: drug delivery and therapeutic applications." FABAD J. Pharm. Sci 32 (2007): 91-100; Ohta et al., Development of a simple method for the preparation of a silica gel based controlled delivery system with a high drug content, European Journal of Pharmaceutical Sciences 26 (2005) 87-96; Akifuddin et al., Preparation, Characterization and In-vitro Evaluation of Microcapsules for Controlled Release of Diltiazem Hydrochloride by Iontropic Gelation Technique, Journal of Applied Pharmaceutical Science Vol. 3 (04), pp. 035-042, April, 2013; Patil et al., A Review On Iontropic Gelation Method: Novel Approach For Controlled Gastric Retentive Gelispheres; International Journal of Pharmacy and Pharmaceutical Sciences, Vol 4, Suppl 4, 2012; Cabellero, et al., Characterization of alginate beads loaded with ibuprofen lysine salt and optimization of the preparation method, International Journal of Pharmaceutics 460 (2014) 181-188; J. M. C. Puguán, X. Yu, H. Kim, Diffusion characteristics of different molecular weight solutes in Ca-Alginate gel beads, Colloids and Surfaces A: Physicochemical and Engineering Aspects (2015), <http://dx.doi.org/10.1016/j.colsurfa.2015.01.027>; Takka and Gurel, Evaluation of Chitosan/Alginate Beads Using Experimental Design: Formulation and In Vitro Characterization, AAPS PharmSciTech, Vol. 11, No. 1, March 2010; Anand, et al., Ion-exchange resins: carrying drug delivery forward, DDT Vol. 6, No. 17 Sep. 2001. See also the Technical Information sheet for Dowex Ion Exchange Resins; the Product Data Sheet for Amberlite IRN78 Resin, both from Dow Chemicals. Also the Technical Sheet for Duolite AP143/1083 Pharmaceutical Grade Anion Exchange Resin (Cholestyramine Resin USP) from Rohm and Haas. The following U.S. Patents and applications are also incorporated by reference in their entireties for all purposes U.S. Pat. Nos. 4,221,778; 4,510,128; 6,322,819; 8,193,211; 8,202,537; 8,771,735; 8,778,398; 8,062,667, and 8,337,890; U.S. Patent Publication Nos. 2003/0180249; 2008/0003267; 2008/0118571; 2012/0076865; 2012/0148672; 2013/0273159; 2014/0004202; 2014/0093578; and 2014/0127306.

As used herein, the term gamma-hydroxybutyrate (GHB) or "oxybate" refers to the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid. The manufacture, use, known dosage forms and dosing can be shown in the above patents. An effective dosage range of Xyrem is 6 g to 9 g, given at night in divided doses approximately 2-4 hours apart. GHB is typically given twice nightly due to a short in vivo half-life. It is subject to a controlled drug distribution system. See U.S. Pat. Nos. 6,472,431, 8,263,

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650, 8,324,275; 8,859,619; 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 8,591,922; and 8,772,306 which are incorporated above.

One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours. As described above, a single dose is eliminated within a shorter period of time. One object of the invention is to maintain the blood level of GHB from about 10 mg/L to about 20 mg/L for up to 8, 7, 6, or 5 hours. Additionally, it is an object of the invention to ensure that the sleep inducing effects of GHB do not remain for longer than the above periods as it would compromise a patient's ability to perform normal day to day activities, such as work or driving a car. One embodiment of the invention is a controlled release formulation of GHB designed to maintain a level of GHB in the blood that satisfies the above criteria. In addition to the controlled or extended release properties of one embodiment, there can be an immediate release GHB formulation that is present in or accompanies the controlled release formulation. A sufficient amount of GHB must be present in the blood to initiate the sleep function of GHB and then the controlled release component may engage to maintain the blood concentration above the threshold for a complete sleep of sufficient duration. It has been discovered that administration of food may extend the effects of GHB in some circumstances and care should be taken to consider this effect during administration. See U.S. Pat. Nos. 8,859,619; 8,778,398 and 8,591,922 as well as U.S. Pat. Publication 2012/0076865 among others.

The buffering capacity of GHB may affect gastric pH and compromise performance of enteric-coated dosage forms. Avoidance of the potential impact on gastric pH is another useful feature of the GHB resinate, since it has no effect on gastric pH.

In one embodiment, the present invention is directed to formulations of drugs that are carboxylic acids, as described herein, and are suited to the controlled release of high dose drugs that are highly water soluble. In addition, in certain embodiments, the formulations described herein provide controlled release of drugs that are highly hygroscopic, even where such drugs must be administered at relatively high doses. In particular embodiments, the controlled release formulations are provided as a unit dose or liquid dosage form.

The formulations and dosage forms of the present invention can also include an immediate release component. The immediate release component can form part of a solid controlled release unit dosage form or liquid dosage form (e.g., combined with a controlled release GHB resinate component) or may be a separate immediate release composition. Therefore, an immediate release component may be provided, for example, as a dry powder formulation, an immediate release tablet, an encapsulated formulation, or a liquid solution or suspension. However, the immediate release component may also be formulated as part of a single dosage form that integrates both the above components. The immediate release component can furthermore be an oxybate salt such as sodium, potassium, calcium, or magnesium, the immediate release component can also comprise the GHB resinate particles without modification to retard release, or a combination of these GHB forms.

In specific embodiments, controlled release and immediate release formulations can be dosed together to a subject to provide quick onset of action, followed by maintenance of therapeutic levels of the drug substance over a sustained period of time. However, because the controlled release component and immediate release component described

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herein need not be present in a single dosage form, as it is used herein, the phrase “dosed together” refers to substantially simultaneous dosing of the controlled release and immediate release components, but not necessarily administration in the same dosage form. Dosing the controlled release and immediate release components together offers increased convenience, allowing patients to quickly achieve and maintain therapeutic levels of a drug over a sustained period of time, while reducing the frequency with which the drug must be dosed. Furthermore, dosing the controlled release and immediate release components together may avoid the disadvantages of dosing regimens and formulations that result in highly pulsatile plasma concentrations.

Gamma butyrolactone (GBL) is a prodrug for GHB. It can be produced by the dehydrogenation of 1, 4 butanediol. GBL can be hydrolyzed under basic conditions (the use of a metal ion hydroxide) to produce GHB. See Arena, C, et al., “Absorption of Sodium γ -Hydroxybutyrate and its Prodrug γ -butyrolactone: relationship between *n* vitro transport and *in vivo* absorption”, *Journal of Pharmaceutical Sciences*, 69(3), (March 1980), 356-358; and Lettieri, J, et al., “Improved Pharmacological Activity via Pro-Drug Modification: Comparative Pharmacokinetics of Sodium γ -Hydroxybutyrate and γ -Butyrolactone”, *Research Communications in Chemical Pathology and Pharmacology*, 22(1), (1978), 107-118.

The required dose of GHB, on a molar basis, is unusually high and quite different from most pharmaceutical agents normally considered for drug-resin complexes. A 9 g dose of sodium oxybate is 71 mMol of oxybate, a carboxylic acid. This stands in contrast to a typical moderately potent active pharmaceutical ingredient (API) having a molecular weight of about 400 daltons and a dose of 400 mg, which results in a molar dose of about 1 mMol. Thus, sodium oxybate dosing is about 70-fold higher (on a molar basis) than a more typical drug.

Much of the dose is required in immediate release form for initial therapeutic benefit. However, due to the buffering effect of oxybate (pKa of 4.5), the immediate-release portion of the dose would cause the gastric pH to increase to about 6. This complicates formulation design, as rate-controlling polymers often have pH-dependent dependent solubility. In particular, if delayed release via enteric coating is desired, then upon release of the immediate release portion of the dose, the concomitant rise in gastric pH could result in at least partial dissolution of the enteric coating, thereby compromising the delayed release function of the enteric coating.

The solubility of sodium oxybate is unusually high. For example, a Xyrem solution is provided as 500 mg/mL concentration in water, or 42 wt %, and its solubility limit is considerably higher. Furthermore, due to the small size and ionic nature of GHB at physiological pH, the drug is unusually mobile in solution. Those skilled in the art will appreciate that these factors complicate and, in many cases, limit conventional approaches for modified release, such as core/shell or matrix formulations, as the high solubility and mobility of GHB would tend to significantly reduce the number of viable approaches using such conventional solubility and diffusivity control technologies.

Furthermore, while extended release oxybate dosage forms are known, such extended release dosage forms are provided as solids, e.g. as tablets. Because the required dose of oxybate is high, such tablets can be quite large, and/or require the administration of multiple tablets. This can be problematic because some patient populations have difficulty swallowing solid dosage forms, or the need to swallow

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multiple tablets may reduce patient compliance. In addition, the sustained release matrix or coating compositions used to provide extended release are complex and expensive to produce. Accordingly, it would be desirable to provide oxybate (or analogous drugs which require administration in high doses) in an extended release, oral liquid dosage form (including suspensions of oxybate-containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user), using simply, readily controlled processing methods.

A drug-resin complex may address some of these limitations, as the drug is essentially insoluble as long as it remains bound to the resin. Instead, the drug release is regulated by exchange with other anions present in the gut, the most prevalent being chloride. Thus, the nature of the formulation challenge is to limit the diffusion of chloride anion into the dosage form rather than to limit the egress of the soluble drug, oxybate.

Drug-resin complexes including modified release drug-resin complexes are known. However, such complexes would typically be considered unsuitable for very high dose, low molecular weight drugs such as oxybate, because the molar amount of drug required is quite high, which would therefore necessitate correspondingly large amounts of ion exchange resin, particularly if the efficiency of binding is significantly less than 100%. Accordingly, for drugs such as oxybate that are dosed at much higher molar levels, e.g., approximately 100-fold higher compared to typical drug dosing, drug-resin complexes would not be considered acceptable.

In one embodiment, a particularly convenient means of administering drug resins is as a suspension of individual drug resinate beads. The beads may be a plurality of individual resin beads, each loaded with drug and optionally coated with a rate-controlling polymer and additives to influence its properties (such as permeability, flexibility, etc.). Coating formulations exist to address processing challenges, such as the swelling of beads and retention of film integrity. One such example is methylphenidate resinate beads as shown in U.S. Patent No. U.S. Pat. No. 8,202,537.

In one embodiment, the present invention provides a GHB formulation which delivers a controlled release profile, for example a controlled release profile suitable for once-a-day dosing as described herein. Due to the prolongation of the drug release, compositions of the present invention are useful because the once-a-day dose provides a more consistent supply (release) of GHB to patients who otherwise may have to take multiple doses a day. In one embodiment, the invention provides a multi-particulate composition, for example a suspension (e.g., homogeneous suspension), or solid compositions such as a tablet, capsule, powder, wafer, or strip system comprised of a plurality of such particles and optionally other excipients.

As used herein, the term “controlled release” refers to compositions, for example GHB resinate compositions as described herein, which are characterized by having at least one of the active components having a release over a period of at least about 2 to about 8 hours, or about 4 to 6 hours, including about 2, about 2.5, about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, about 7, about 7.5, or about 8 hours, inclusive of all ranges therebetween. The release profile may be assessed using *in vitro* dissolution assays known to those of skill in the art, e.g., USP apparatus 2 (paddle) or, more preferably, apparatus 4 (flow-through cell). Particularly when the molar dose of oxybate is large and approaches the amount of anion in the

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dissolution media, a flow-through apparatus is desired so that the media composition and flow rate can better approximate the physiologic state. The release profile can be assessed for example (e.g., for bioavailability determinations), in pharmacokinetic studies using plasma concentrations to assess maximum concentration (C_{max}) and area under the curve (AUC). Such assays are well known to those of skill in the art.

In one embodiment, the present invention provides a drug-ion exchange resin composition for further use in a formulation with conventional pharmaceutically acceptable components to provide ingestible compositions. The finished dose compositions may take the form of liquid preparations, such as suspensions, or solid preparations such as tablets, capsules, liquisols, powders, wafers, strips, etc.

Ion-exchange matrices suitable for use in these preparations are water-insoluble and comprise in most embodiments a pharmacologically inert organic and/or inorganic matrix containing functional groups that are ionic or capable of being ionized under the appropriate conditions of pH. In one embodiment, the ion-exchange matrix is anionic. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene, etc.), or partially synthetic (e.g. modified cellulose and dextrans). The inorganic matrix, in various embodiments, can comprise silica gel modified by the addition of ionic groups, or other similar inorganic materials functionalized with ionic groups. Covalently bound ionic groups may be strongly acidic (e.g., sulfonic acid, phosphoric acid), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., primary amine), weakly basic (e.g. quaternary ammonium), or a combination of acidic and basic groups. In general, the types of ion exchangers suitable for use in ion-exchange chromatography and for such applications as deionization of water are examples of materials suitable for use in the controlled release of drug preparations. Such ion-exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp: 312-343) and "Techniques and Applications of Ion-Exchange Chromatography" (pp: 344-361) in Chromatography. (E. Heftmann, editor), van Nostrand Reinhold Company, New York (1975). A high exchange capacity is desired to limit quantities of resin needed, and that typical values are about 4 meq/g

In one embodiment, the size of the ion-exchange particles is from about 5 microns to about 1,000 microns. In most embodiments the particle size is within the range of about 50 microns to about 750 microns (including about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 550, about 600, about 650, about 700, or about 740 microns, inclusive of all values and ranges therebetween) for liquid dosage forms, although particles up to about 1,000 micron (including the values and ranges herein, and in addition about 800, about 850, about 900, about 950, or about 1000 microns, inclusive of all values and ranges described herein) can be used for solid dosage forms, e.g., tablets and capsules. Particle sizes substantially below the lower limit are generally difficult to handle in all steps of the processing. Both uncoated and coated drug-ion exchange resin particles may be designed within this size range.

Both regularly and irregularly shaped particles may be used as resins. Regularly shaped particles are those particles that substantially conform to geometric shapes such as spherical, elliptical, cylindrical and the like, (e.g., three dimensional shapes readily described by a three dimensional space group) which are exemplified by (but not limited to) any of the ion exchange resins disclosed herein, for example

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Dow XYS-40010.00 and Dow XYS-40013.00 (The Dow Chemical Company). Irregularly shaped particles are all particles not considered to be regularly geometrically shaped (for example not readily described by a three dimensional space group), such as particles with amorphous shapes and particles with increased surface areas due to surface channels or distortions. Irregularly shaped ion-exchange resins of this type are exemplified by (but not limited to) any of the ion exchange resins disclosed herein, for example Amberlite IRP-69 (Rohm and Haas). Two of the resins of some of the embodiments of this invention are Amberlite IRP-69 and Dow XYS-40010.00. Both are sulfonated polymers composed of polystyrene cross-linked with about 8% of divinylbenzene, with an ion-exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H^+ -form). Their essential difference is in physical form. Amberlite IRP-69 consists of irregularly shaped particles with a size range of about 5 microns to about 149 microns produced by milling the parent large size spheres of Amberlite IRP-120. The Dow XYS-40010.00 product consists of spherical particles with a size range of 45 microns to 150 microns.

In one embodiment, suitable ion-exchange resins include anion exchange resins, such as have been described in the art and are commercially available. These resins are particularly well suited for use with acidic drugs including GHB, as well as prodrugs such as GBL, salts, isomers, polymorphs, and solvates thereof, as well as other acidic drugs identified herein and/or known in the art such as salicylates, nicotinic acid, mefenamic acid, methotrexate, furosemide, phenolic drugs such as paracetamol, morphine, and levothyroxine, warfarin, phenylbutazone, indomethacin, barbiturates, phenytoin, sulphonamides, etc.

Any anion exchange suitable for pharmaceutical use can be employed in the compositions of the present invention, particularly strong anion exchange resins. An example of a suitable anion exchange resin is a cholestyramine resin, a strong base type 1 anion exchange resin powder with a polystyrene matrix and quaternary ammonium functional groups. The exchangeable anion is generally chloride which can be exchanged for, or replaced by, virtually any anionic species. Other examples include Type II resins, which contain dialkyl 2-hydroxyethyl ammonium chloride or hydroxide groups. Such Type I and Type II resins are available under the DOWEX® and Amberlite® trade names. A commercially available Cholestyramine resin is PUROLITE® A430MR resin. As described by its manufacturer, this resin has an average particle size range of less than 150 microns, a pH in the range of 4-6, and an exchange capacity of 1.8-2.2 eq/dry gm. Another pharmaceutical grade cholestyramine resin is available as DUOLITE® AP143/1094 (Rohm and Haas/Dow), described by the manufacturer as having a particle size in the range of 95%, less than 100 microns and 40%, less than 50 microns. The commercial literature from the suppliers of these and other resin is incorporated herein by reference (PUROLITE A-430 MR; DOW Cholestyramine USP, Form No. 177-01877-204, Dow Chemical Company; DUOLITE AP143/1083, Rohm and Haas Company, IE-566EDS—February 06). Other suitable anion exchange resins include POROS® XQ anion exchange resins available from ThermoFisher Scientific. Both regularly and irregularly shaped particles may be used as resins. Regularly shaped particles are those particles that substantially conform to geometric shapes such as spherical, elliptical, cylindrical and the like, (e.g., three dimensional shapes readily described by a three dimensional space group) Irregularly shaped particles are all particles not considered to be regularly geometrically shaped (for

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example not readily described by a three dimensional space group), such as particles with amorphous shapes and particles with increased surface areas due to surface channels or distortions. The regular and irregularly shaped particles can comprise any of the anion exchange resins disclosed herein.

For the oxybate resinate compositions of the present invention, the amount of oxybate present in the resinate should be high to minimize the amount of resin required. Furthermore, in most embodiments, the amount of GHB resinate administered, expressed as GHB mEq (i.e., mmoles) is about 20 to about 120 mEq, including about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, or about 120 mEq, inclusive of all values and ranges therebetween.

The selected ion-exchange resins may be further treated by the manufacturer or the user to maximize the safety for pharmaceutical use or for improved performance of the compositions. Impurities present in the ion-exchange resins may be removed or neutralized by the use of common chelating agents, anti-oxidants, preservatives such as disodium edetate, sodium bisulfate, and so on by incorporating them at any stage of preparation either before complexation or during complexation or thereafter. These impurities along with their chelating agent to which they have bound may be removed before further treatment of the ion exchange resin with a compound to slow drug release and coating with a diffusion barrier.

Various analogous binding reactions can be carried out for binding an acidic drug to an anion exchange resin. These are (a) resin (Cl^- form) plus drug (salt form); (b) resin (Cl^- form) plus drug (as free acid); (c) resin (OH^- form) plus drug (salt form); (d) resin (OH^- form) plus drug (as free acid); (e) resin (OH^- form) plus prodrug (γ -butyrolactone). All of these reactions except (d) and (e) have ionic by-products and the anions generated when the reactions occur compete with the anionic drug for binding sites on the resin with the result that reduced levels of drug are bound at equilibrium. For acidic drugs, stoichiometric binding of drug to resin is accomplished only through reactions (d) and (e). The binding may be performed, for example as a batch or column process, as is known in the art.

Typically the drug-ion exchange resin complex thus formed is collected by filtration and washed with appropriate solvents to remove any unbound drug or by-products. The complexes can be air-dried in trays, in a fluid bed dryer, or other suitable dryer, at room temperature or at elevated temperatures which would not degrade the complex.

In one embodiment, the complexes of the present invention can be prepared by batch equilibration, in which a solution of the drug is contacted with finely divided ion-exchange resin powders. While ion exchange resins are typically provided in very fine particle sizes, which render conventional columnar ion-exchange processes inefficient, such methods can be used for ion exchange resins of suitable particle size. The total ion-exchange capacity represents the maximum achievable capacity for exchanging cations or anions measured under ideal laboratory conditions. The actual capacity which will be realized when loading a drug onto ion exchange resin will be influenced by such factors as the inherent selectivity of the ion exchange resin for the drug, the drug's concentration in the loading solution and the concentration of competing ions also present in the loading solution. The rate of loading will be affected by the activity of the drug and its molecular dimensions as well as the extent to which the polymer phase is swollen during loading.

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In one embodiment, a batch or equilibrium process is used to load a drug onto an ion-exchange resin. It is usually desirable to load as much as possible of the drug, such as GHB or GBL, onto the ion exchange resin, as typical GHB doses required for treating excessive daytime sleepiness and cataplexy in patients with narcolepsy are quite high. Low loadings of GHB in the resinate would require quite large amounts of resin, resulting in unit dosages which would be too large to be conveniently administered and resin quantities that may give rise to more adverse effects such as gastrointestinal disturbance. Complete transfer of the drug from the loading solution into the ion-exchange resin is not likely in a single equilibrium stage. Accordingly, more than one equilibration may be required in order to achieve the desired loading onto the ion exchange resin. The use of two or more loading stages, separating the resin from the drug-containing liquid phase between stages, is a means of achieving maximum loading of the drug onto the ion exchange resin, although some loss of drug from the liquid phase of the final loading stage may occur.

The efficiency of loading the drug (e.g. GHB) onto the ion exchange resin can be influenced by the counter ion used in the ion exchange resin. Commercially supplied anionic resins for pharmaceutical use are almost exclusively in the chloride form. However, chloride ions have a much higher affinity for the exchange site in the resin relative to GHB. The affinity can be estimated based on the pK_a of GHB (4.44) relative to other short-chain fatty acids for which affinities are known. On that basis, GHB has approximately 18% affinity relative to chloride on the anion exchange resin. Bicarbonate, on the other hand, has an affinity of about 27% affinity relative to chloride. Therefore, when a bicarbonate-exchanged resin is contacted with GHB, a much higher efficiency of GHB incorporation may be achieved, because the affinity of GHB relative to bicarbonate is about 67% vs. about 18% relative to chloride. Other "intermediate" exchange anions can also be used, especially those with low affinity relative to chloride and much lower cost relative to oxybate. Thus in some embodiments, substantially all of the chloride counter ion of the e.g. commercially available pharmaceutical grade anion exchange resin is replaced with the intermediate anion (e.g. bicarbonate), in one or more batch equilibration steps as required. After rinsing with an appropriate solvent, the ion exchange resin exchanged with the lower affinity anion (relative to chloride) can then be then exchanged with oxybate.

Substantially complete incorporation (i.e., expressed as the percentage of theoretically available ion exchange sites) of oxybate in the anion exchange resin is desirable to minimize the amount of anion exchange resin required to provide a specified dose of drug (e.g. oxybate). In practice, 100% incorporation of the drug can be difficult and/or expensive to achieve, so somewhat less than substantially complete levels of incorporation of drug are also suitable. Typically, levels of incorporation of more than about 75% are acceptable, including about 75%, about 80%, about 85%, about 90%, about 92%, about 94%, about 96%, about 98%, about 99%, or about 100%, inclusive of all values and ranges therebetween.

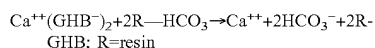
When a multi-step batch equilibration is needed or desirable, the resinate slurry formed during equilibration can be decanted to remove the solution of oxybate. The decant can be collected for potential recovery of oxybate or waste disposal. The resinate is then rinsed with solvent, such as de-ionized water, and then charged to the batch equilibration tank where it is contacted with fresh or recovered oxybate to increase the level of incorporation of oxybate. Multiple

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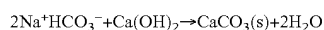
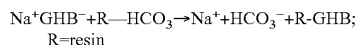
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equilibration steps can be used with fresh or recycled oxybate solution until the desired level of incorporation, as described herein, is achieved.

Recovery of oxybate from a chloride-exchange process can be very challenging due to oxybate's high water solubility and relatively small size. If aqueous processing is used, all chloride salts are soluble. However, when an intermediate anion (e.g. bicarbonate) is used, the solubility can be manipulated with selection of the cationic form of oxybate. If full and complete exchange of oxybate is desired in one step, then the salt form of oxybate is selected such that the salt form of the exchanged anion is insoluble. For example, calcium salts of many exchangeable anions tend to have very low solubilities. Oxybate can be introduced as calcium oxybate, which is highly water-soluble and suitable for an aqueous exchange process. Precipitation drives the exchange process to near-completion, resulting in very high oxybate yield and incorporation. For example, bicarbonate would precipitate as calcium carbonate if the relatively insoluble calcium hydroxide is added in stoichiometric amount at the commencement of batch equilibration, as shown below. Other example intermediate examples include phosphate (precipitating as calcium phosphate), sulfate (precipitating as calcium sulfate), and hydroxide (precipitating as calcium hydroxide).



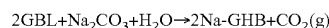
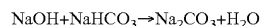
Use of precipitation as a means to drive batch equilibration can result in some difficulties in recovering the resin, as the resinate and precipitate can both be small particles. In some embodiments, the exchange process is carried out under conditions such that all species remain soluble, and therefore the resinate and solution are easily separated. Next, the oxybate is recovered from the solution in a separate vessel by performing a displacement precipitation by addition of another salt or base. For instance, in the above example, the calcium hydroxide can be added in a separate step, thereby avoiding a difficult separation problem. Although this process may provide a somewhat less efficient equilibration per batch cycle, recovery of the un-exchanged oxybate can be nearly 100%, and multiple batch equilibrations can be performed economically. The technique can be more generally applied if sodium oxybate is used in the exchange process, because most sodium salts of the exchanged anion would remain soluble. In the recovery step, a calcium salt or base is added in near-stoichiometric amount to precipitate the exchanged oxybate and enable full recovery of the sodium oxybate. In one embodiment, calcium hydroxide is added to facilitate recovery. Because it has low solubility, calcium hydroxide can be used in excess without appreciably contaminating the recovered sodium oxybate with calcium.



In yet another embodiment of processes for forming the GHB resinate, the anion can be recovered by sub-stoichiometric addition of the soluble calcium oxybate to the sodium-exchanged intermediate anion in the recovery process. Most of the sodium oxybate can be recovered and recycled without causing precipitation during the batch equilibration.

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In a particular embodiment, bicarbonate can be evolved as CO_2 gas and the sodium ions form sodium oxybate by adding GBL. This avoids a potentially difficult separation of precipitate during recovery. The sodium bicarbonate is first converted to sodium carbonate, and then the sodium carbonate is reacted with GBL to yield sodium oxybate and carbon dioxide as shown below.



In yet another embodiment, the bicarbonate form of an anion exchange resin (e.g., and type 1 strong base anion exchange resin), prepared, for example by ion exchange of the chloride form with sodium or potassium bicarbonate (or other soluble bicarbonate salts), is equilibrated with a solution of sodium or potassium oxybate. The resulting oxybate resinate can be separated from the oxybate equilibration solution by known methods (decanting, filtering, etc.). The oxybate equilibration solution can then be treated with sodium or potassium hydroxide to increase the pH, and then contacted with GBL. At the elevated pH, the GBL reacts with exchanged bicarbonate to form additional GHB (oxybate) and carbon dioxide, thereby regenerating the oxybate equilibration solution so that it can be reused, as the bicarbonate ions produced during the initial ion exchange/equilibration step is lost as carbon dioxide gas. The regenerated oxybate equilibration solution can then be re-equilibrated with the oxybate resinate formed in the initial equilibration step, so as to further increase the degree of exchange of oxybate in the resinate. The regenerated equilibration solution can be further regenerated, and further equilibrated with the oxybate resinate as many times as is needed or desired to obtain the desired degree of incorporation of oxybate in the oxybate resinate. A further advantage of this method is the minimization of oxybate waste due to the ability to regenerate and recycle the oxybate equilibration solution.

High loading capacity will be favored by high charge density in the drug. A high loading rate is favored by lower molecular weight. Higher drug concentrations in the loading solution, with a minimum of competing ions, will also favor higher adsorption capacity.

Thus, in one aspect, the invention provides drug-ion exchange resin complexes comprising a drug loaded in an ion exchange resin as described herein. The drugs and ion exchange resins may be readily selected from amongst those drugs and resins described herein. In most embodiments, GHB and GBL are suitable drugs. The invention further provides drug-ion exchange resin matrixes defined as follows.

The drug-ion exchange resin complexes of the present invention can readily be formulated with pharmaceutically acceptable excipients according to methods well known to those of skill in the art, for example as described in Remington, The Science and Practice of Pharmacy, 22 Edition Philadelphia College of Pharmacy 2013 Pharmaceutical Press, herein incorporated by reference in its entirety for all purposes. In one embodiment, these formulations contain a substantially coated drug-ion exchange resin complex of the invention, optionally with a compound that will slow the release of the drug. In another embodiment, such formulations may also contain a selected amount of uncoated drug-ion exchange resin complex, optionally with a compound to slow the release as described herein. In certain formulations, mixtures of coated drug-ion exchange resin complexes and uncoated drug-ion exchange resin complexes

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are present. These formulations may contain any suitable ratio of coated to uncoated product.

In one embodiment, the controlled release dosage form includes drug loaded onto beads (e.g., ion-exchange beads) in combination with one or more optional excipients, such as binders, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, lubricants, glidants, or other suitable excipients. In one embodiment of the compositions of the present invention that can be fashioned into a tablet or other solid form, beads containing GHB or GBL can include one or more binders that are known for use in tablet formulations. In one such embodiment, the solid form may include at least one binder selected from hydroxypropyl cellulose (HPC), ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate. In specific embodiments, the solid form included in a controlled release dosage form as disclosed herein may comprise binder levels ranging from approximately 1% to 10% by weight. For example, the CR core may include a binder in an amount selected from about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, and 10% by weight, including all ranges therebetween. In certain such embodiments, the amount of binder included in the CR core may range from about 1 to 2%, 1 to 3%, 1 to 4%, 1 to 5%, 1 to 6%, 1 to 7%, 1 to 8%, 1 to 9% and 1 to 10% by weight.

One formulation of the present invention may include one or more lubricants to improve desired processing characteristics. One embodiment of the present invention may include one or more lubricants selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added in a range of about 0.5% to 5% by weight. Particular embodiments may comprise a lubricant in a range of about 0.5% to 2% by weight, about 1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight, inclusive of all ranges therebetween. Still lower lubricant levels may be achieved with use of a "puffer" system during tableting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation. When "puffer" systems are used for tableting, the compositions of the present invention can, but need not be, substantially free of lubricant (e.g., include only traces of lubricant deposited by contact with the lubricant coated tablet press).

In certain embodiments, where the compositions of the present invention are provided as liquid compositions, such as suspensions, the compositions of the present invention can further comprise colorants, flavoring agents (natural and artificial), stabilizing agents (EDTA salts, parabens, benzoates), thickeners (tragacanth, xanthan gum, bentonite, starch, acacia, celluloses), humectants, sweeteners (sucralose, acesulfame K, saccharides, sorbitol, xylitol, mannitol, maltose), etc.

In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or

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buffering agent. Such agents may be acids, bases, or combinations thereof. In certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alpha-hydroxy carboxylic acid. In certain other embodiments, the acid is selected from the group including, but not limited to, acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like. In a preferred embodiment, the acid is malic or hydrochloric acid. In certain other embodiments, the pH adjusting agent may be a base selected from the group including, but not limited to, acetanilide, ammonia, apomorphine, atropine, benzocaine, caffeine, calcium hydroxide, cocaine, codeine, ephedrine, morphine, papaverine, physostigmine, pilocarpine, potassium bicarbonate, potassium hydroxide, procaine, quinine, reserpine, sodium bicarbonate, sodium dihydrogen phosphate, sodium citrate, sodium titrate, sodium carbonate, sodium hydroxide, theobromine, thiourea or urea. In certain other embodiments, the pH adjusting agent may be a mixture of more than one acid and/or more than one base. In other preferred embodiments, a weak acid and its conjugate base are used to form a buffering agent to help stabilize the composition's pH.

In certain embodiments, the pharmaceutical composition may also contain an antioxidant. An "antioxidant" is understood herein to mean certain embodiments which are substances that inhibits oxidation. Such antioxidants include, but are not limited to, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite, anoxomer and maleic acid BP.

The drug-ion exchange resin composition thus prepared may be stored for future use or promptly formulated with conventional pharmaceutically acceptable carriers to prepare finished ingestible compositions for delivery orally, or via other means. In one embodiment, a tablet of the invention is formulated as an orally disintegrating tablet. Such orally dissolving tablets may disintegrate in the mouth in less than about 60 seconds. See U.S. Patent Publication. 2012/0076865.

In one embodiment, the oral liquid compositions of the present invention may also comprise one or more surfactants in amounts of up to about 5.0% w/v or from about 0.02 to about 3.0% w/v of the total formulation. The surfactants useful in the preparation of the finished compositions of the present invention are generally organic materials which aid in the stabilization and dispersion of the ingredients in aqueous systems for a suitable homogenous composition. In particular embodiments, suitable surfactants are non-ionic surfactants such as poloxamers, polyoxyethylene ethers (BRIJ), alkoxylated fatty acids (MYRJ), polysorbates (TWEENS), macrogol mixtures (Gelucire, Labrasol), and sorbitan esters (SPANs). These are produced in a wide variety of structures and molecular weights.

When present, the surfactant component may comprise from about 0.01 to about 2.0% w/v of the total composition (for example 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2.0% w/v, inclusive of all ranges therebetween) and in particular embodiments will comprise about 0.1% w/v of the total of the composition.

One or more additional emulsifiers or surfactants can also be employed in one embodiment of the invention.

The sustained-release profiles of drug can be obtained by using a mix of uncoated and semipermeable coated resins and by selecting the degree of cross-linking and particle size of the resins without a coating process. Examples of ion exchange resins include simple resins (i.e., uncoated drug-ion exchange resin complexes), microencapsulated or coated resins (i.e., coated drug-ion exchange resin complexes), hollow fiber systems (i.e. hollow fibers with drug containing lumen), sigmoidal-release systems. Examples of such drugs are frusemide, cyclosporin, allopurinol and ciprofloxacin. See Mahore et al. Formulation of such drugs as resins according to the present invention permits particle sizes that make such release characteristics (e.g., sigmoidal) feasible at reasonable coating weights.

Some embodiments of the present invention involve direct synthesis of oxybate resinate from one or more precursors. Using a hydroxide-form Type 1 strong base anion exchange resin, essentially 100% loading efficiency can be achieved with a simple aqueous reaction with GBL.

The ability to prepare an oxybate resinate, at high loading, in a one step process from GBL can be amenable to point-of-use synthesis (either in patient's hands or at clinical site), as it does not involve shipping or handling the regulated API (GHB). Such a direct synthesis can be carried out using a batch or equilibrium process as described herein, wherein a GBL loading solution is contacted with the particulate hydroxide-form strong base anion exchange resin. The GBL reacts in situ to form an ionic complex of oxybate with the ion-exchange resin, and releasing water as a by-product. It is possible to get 100% yield as well as 100% loading efficiency (i.e., oxybate ionically bound to 100% of the available binding sites) on the resin by such processes. For example, loading efficiencies higher than about 65% (e.g., 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, or about 100%, including ranges therebetween, can be achieved). Because GBL is uncharged and the reaction does not produce ionic byproducts, there are no anions to compete for reaction on the site. Such conditions can achieve 100% reaction on the resin, so the hydroxide-form resin can be used safely, whereas in other applications this may not be possible for patient safety reasons because any unexchanged hydroxide would leave the resin as sodium hydroxide, raising the pH at site of delivery and potentially causing gut wall irritation.

The one-step process is also advantageous because it simplifies purification of the GHB resinate. Because the reaction occurs on the resin and not in the bulk solution, any byproducts that would be made are rinsed off the product. These include any of the impurities in the GBL starting material, as well as unreacted GBL.

Because of the unusually large molar amount of GHB in the compositions of the present invention, relative to the molar quantity of anion present in the gut, the present inventors have found that the compositions of the present invention can provide sustained release without the use of diffusion controlling coatings on the resinate particles. The present inventors have recognized that because the volume and anion content of gastric juice in the fasted state is lower than the molar dose of GHB required for treating the conditions described herein, the rate of GHB release is strongly influenced by the rate of physiological production of anions, and therefore suitable GHB release profiles can be provided without the use of diffusion controlling coatings. For example, while the resinate beads are retained in the stomach, the release of GHB from the resinate beads pro-

vided by ion exchange with gastric ions (mainly Cl^-) can be limited by the rate of stomach acid secretion. Similarly, as the resinate beads transit the duodenum and small intestine, the remaining dose of bound GHB can exceed local anion capacity. Thus, the rate of GHB release can be limited by the rate of secretion or diffusion of anions into the gut.

The basal anion capacity of the GI tract is quite small. As summarized in McConnell (Int J Pharm 2008, 364: 213-226, Table 1), fasted state basal values of bile salts are so low that they may be ignored. The fasted state chloride balances are 4.6 mEq in the stomach and 13.1 mEq in the small intestine. Compared to an oxybate dose of about 100 mEq, there is almost an order of magnitude deficiency in resident anion capacity for exchange. Such a situation would not occur with the vast majority of drugs having doses in the <1 mMol range.

	Stomach	Small intestine
Volume, mL	45	105
Chloride, mM	102	125
Total mEq	4.6	13.1

Therefore, the present inventors have discovered that the release of the ion-exchange resin-bound oxybate can be limited by secretions of anions in the GI tract, of which chloride is dominant. In the stomach, basal acid output (as chloride) is about 3 mEq/h in the fasted state. Even in the event that fed-state behavior is induced upon dosing, the fed state maximum secretion is only about 25 mEq/h. Therefore, the stomach cannot support full exchange at rates required to impart a meaningful duration of effect.

Chloride is actively secreted in jejunum, at a rate of about 4 mEq/h/30 cm under conditions where 120 mM chloride is already present. (Davis G R, et al, Active chloride secretion in the normal human jejunum, J Clin Invest 66:1326-1333 (1980)) This translates to a basal rate of about 32 mEq/h in absence of a chloride gradient. In presence of a gradient, the present inventors have found that the contribution of passive diffusion can be sufficient, but may still provide a meaningful impediment to full and timely release of oxybate from the resin.

In the ileum, chloride secretions are substantially less, as characterized by Turnberg. (Turnberg L A et al, Interrelationships of chloride, bicarbonate, sodium, and hydrogen transport in human ileum, J. Clin Invest, 49: 557-567 (1970)). Most chloride secretion is associated with bicarbonate exchange when levels are high. One skilled in the art would appreciate that the perfusion studies by Turnberg indicate that chloride secretion in the ileum would almost certainly be insufficient to support the required exchange with GHB-resinate. For example, even in the extreme case where bicarbonate is almost 90 mM and chloride is only 40 mM, the chloride secretion—taking into account the whole length of ileum—would be expected to be at most 23 mEq/h. In the more typical case where bicarbonate is 40 mM, chloride is actually absorbed rather than secreted—even when chloride levels are set at 40 mM. Yet ileal fluid is maintained isotonic.

To further add to the limitations of biology, the reservoir of small intestinal fluid is small and not well distributed. Only about 10% of the physical volume of the small intestine is filled with fluid. The fluid is not continuously and evenly distributed, as reported by Schiller (Schiller C, et al, Intestinal fluid volumes and transit of dosage forms as

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assessed by magnetic resonance imaging, *Aliment Pharmacol Ther* 2005; 22:971-979) but rather the majority of fluid exists in about 4 fluid pockets that access a relatively small amount of available surface area. This is not very limiting for non-resinate dosage forms, as long as drug dissolution can occur, as once the drug is dissolved, it can access most of the surface area of the small intestine for absorption. A resinate, on the other hand, requires exchange with dissolved anions in order to provide release of the drug. As exchange occurs, oxybate is released to, and chloride is depleted from, the surrounding fluid. Further exchange is limited until oxybate is absorbed and chloride is replenished in the surrounding fluid—both processes that require fluid contact with intestinal surface. Therefore, if only 10% of the intestinal surface is physically available at any given time, the rate of chloride replenishment must be 10-fold higher to reliably compensate. One skilled in the art considering these unusual aspects would conclude that, in the face of insufficient resident anion capacity in the small intestine, a resinate dosage form would not release its drug completely and, furthermore, what release occurs may not be well-regulated.

Given the above observations, permeability and amount of film may require adjustment to achieve the intended release profile.

Optionally, the release of GHB can be tailored by changing the bead size and/or degree of crosslinking of the beads to provide additional resistance to diffusion. For example, larger resinate beads have a lower surface area/volume ratio than smaller resinate beads, and therefore would release GHB more slowly than the smaller beads in the presence of a solution of the same ionic strength. Similarly, the degree of crosslinking of the beads relates to the degree of swelling of the beads, which in turn is related to the rate at which ion exchange, and this drug release can occur. Specifically, more highly crosslinked beads swell less, and thus have slower ion exchange kinetics, compared to less highly crosslinked beads. Thus, the kinetics of drug release can also be controlled by manipulating the degree of crosslinking of the beads. Effects of particle size, particularly 100 microns or greater, and crosslinking, particularly 4% or greater, that may be modest under normal circumstances may be more impactful in the absence of a rate-controlling coating and when gut anion concentrations are substantially diminished.

If no diffusion controlling coating is required, other processing schemes for making the resinate can be considered to improve manufacturing flexibility. For example, instead of using ~100 micron beads, the drug (e.g., GHB or GBL) can be loaded onto larger beads (e.g., 600 micron beads), and then ground to the desired particle size, particle size distribution, consistency, etc. to select or control the desired release characteristics. This could be carried out in an aqueous suspension, so that no isolation or drying of the resinate would be needed. Moreover, if there is no need to coat the particles (e.g., with a diffusion for coating), the irregular shape or dispersity in size distribution of ground particles, which is normally a complicating factor for coating processes, is not an issue.

In other embodiments, the compositions of the present invention can provide differential displacement of drug (e.g. oxybate) from the resinate. Core/shell release characteristics in the resinate beads can be provided by (a) loading oxybate onto an ion exchange resin such that complete loading is achieved, then (b) coating the beads with a portion of lipophilic agent (i.e. lipophilic anion) having much higher selectivity for the ion-exchange resin than GHB. The lipophilic agent will deposit in the outer shell, at the first sites it contacts, and will be relatively immobile resulting in

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reversible blockage of the bead pores. Suitable lipophilic agents would be, for example, sulfate salts of medium or long-chain fatty acids, such as sodium lauryl sulfate (SLS), or sulfonic esters, such as dioctyl sulfosuccinate (docusate). Other suitable agents may include alkylbenzene sulfonates, 2-naphthalene sulfonate, phenol, salicylic acid, or any other species that may bind more strongly to the resin than oxybate. In particular embodiments, the lipophilic agents are those which are bulky or present hydrophobic tails that may further hinder diffusion of chloride into the resin pore, or oxybate out of the pore after exchange. Although many effective agents may, in other contexts present toxicity concerns, because such agents are strongly bound to the resin, exposure of the agent to the patient is limited. In one embodiment, the lipophilic agent acts as a diffusion barrier both by blocking pores and by facilitating pore blockage by other hydrophobic agents, for example those added during manufacturing, or which may be present in the patient's digestive tract after administration. For example, if sufficient amounts of a surfactant such as SLS is employed, then a non-ionic hydrophobic agent may be more effectively introduced into the bead pore volume due to its compatibility with the hydrophobic "tail" of the SLS molecule. This provides retarded initial release of the drug (e.g., GHB). In other embodiments, further heat treating of the resinate beads can reduce the variability of release, or further retard release. In other embodiments the compositions of the present invention can comprise more than one population of beads, in which one or more of the bead populations is treated with a lipophilic agent, a combination of a lipophilic agent and a hydrophobic agent, or heat treated to as to provide the desired release characteristics. For example, untreated beads would provide more immediate or faster release, and treated beads would provide delayed or slower release.

If further control of release is needed, in a further embodiment the present invention provides a novel method for preparing GHB-containing resinate beads coated with a diffusion rate controlling coating. This embodiment takes advantage of the driving force supplied by reaction of GBL on the active (hydroxide-bearing) sites of hydroxide-form ion exchange resin beads, and the relatively high diffusion characteristics of the small and uncharged GBL molecule. Hydroxide-form ion-exchange resin beads (of any size) can be coated with a flexible film, such as PVAcetate, Eudragit RS, cellulose acetate 398, a mixture of Eudragit RS/RL or Eudragit NE, ethylcellulose, or an enteric such as Eudragit L100, L55 or FS100 with suitable plasticizer. The coated ion-exchange resin beads are then suspended in de-ionized water to equilibrate. GBL is introduced to the suspended beads, which then diffuses through the rate-controlling film, and reacts progressively with the OH-bearing sites within the resin. Sufficient batch equilibration time is provided to ensure complete reaction. The excess GBL is washed off, and the resulting wet resinate beads have a sustained release coating over GHB resinate, which were formed without starting with GHB resinate. This process may be useful for point-of-use preparation, or can improve the utilization of GBL in preparing the product: no GHB or GBL is lost due to processing during coating, as no GBL is present during the coating process.

In one embodiment of the present invention, the present formulation is administered to a patient once nightly. The patient is administered between 4 g and 10 g GHB/day, or 6 g and 9 g/day. Any of the compositions described herein can be used to provide retarded or delayed release of GHB. For example, the GHB resinate beads may be presented in

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hydrated form as part of an aqueous suspension, or may be provided as dried beads for mixing with water immediately prior to ingestion or to be taken without water (e.g., as a powder, tablet, capsule etc.). As discussed herein, Type 1 strong base anion exchange resins swell in the presence of water, to an extent that depends on the degree of crosslinking and the nature of the anion bound to it. In the dried state, the sustained release resinate beads of the present invention can hydrate more slowly if release-retarding agents are used. As the beads hydrate, the diffusion of physiologically produced anions of the gastrointestinal tract (e.g. mainly chloride) into the beads can accelerate, thus producing a delayed or gradually increasing rate of release of oxybate.

In another embodiment, a water permeable but relatively insoluble coating is employed over the dry resinate beads such that, when the dry beads are suspended in water, water diffuses through the coating to hydrate and swell the resinate beads. The resulting expansion of the beads causes the coating to rupture, and allow release of the GHB. Suitable polymers for preparing such coatings include one or more of cellulose such as ethyl cellulose, cellulose acetate, cellulose phthalate; polyvinyl acetate, acrylic polymers and copolymers such as those available under the Eudragit® trade name (e.g., Eudragit® NE30D, RL, and RS resins). Such coatings can be plasticized or unplasticized, and coated onto the beads using methods well-known in the art (pan coating, fluidized bed coating, etc.).

As discussed herein, the dose of GHB required for treating excessive daytime sleepiness and cataplexy in patients with narcolepsy is quite high, resulting in the administration not only of relatively large masses of GHB composition, but also water required for administration (particularly when the GHB composition is aqueous). However, since oxybate is administered at night, administering large quantities of water can cause bed-wetting. Accordingly, if administered as an aqueous suspension, the highest practical solids loading is desired. The factors which affect the solids loading (volume fraction) of the suspension include the medium used for dilution (water vs. alcohol) and its viscosity, the degree of swelling of the resinate, the sphericity and uniformity of the beads, and surface charge. See Seno and Yamabe, *The Rheological Behavior of Suspensions of Ion-Exchange Resin Particles*, Bulletin of the Chemical Society of Japan Vol 39, 776-778 (1966), herein incorporated by reference in its entirety for all purposes. In various embodiments, the compositions of the present invention can be administered as suspended resinate particles in a gel, suitable for ingestion by squeezing from a pouch. In other embodiments, the compositions of the present invention can be dosed in two stages: an initial loading dose followed by a chasing dose. Both the loading and chasing dose comprise suspended beads, but the chasing dose is less concentrated. In still other embodiments, the GHB resinate beads can be administered dry, e.g. by having the patient suck the dry beads through a tube or straw. In such embodiments, an added glidant, which is an excipient used in the art to facilitate powder flow by reducing interparticle friction and cohesion, can be used to facilitate administration. They are used in combination with lubricants as they have no ability to reduce die wall friction. Non-limiting examples include fumed silica, talc, and magnesium carbonate.

The oxybate resinate compositions of the present invention can include an immediate release and an extended release component of oxybate. Such compositions can include, for example, a combination of a population of uncoated resinate beads and a population of resinate beads with a diffusion rate controlling coating as described herein;

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a single resinate bead population that provides immediate release by ion exchange with physiological anions (e.g. chloride), followed by extended release of oxybate controlled by physiological production of e.g. chloride; combinations of populations of resinate beads having different particle sizes and/or crosslinking densities to control release; or any combination of immediate release and extended release resinate beads disclosed herein.

In one embodiment, the compositions of the present invention may be an immediate-release alternative to Xyrem®. Xyrem® has a steep dose-response curve, and inadvertently taking two doses at the same time would have an adverse effect on the patient. If sodium oxybate is instead provided in resinate form for immediate release, as described herein, the capacity of the stomach and small intestine to provide exchangeable anion would limit the consequences of an inadvertent overdose. A 4.5 g dose of Xyrem is 35.7 mEq oxybate. If the stomach has about 5 mEq chloride, then about 30 mEq of additional exchangeable anion must be provided with the resinate formulation of the present invention to ensure complete release of oxybate. This can be achieved by inclusion of exchangeable anion in the formulation, for example glycine or other amino acids, chloride, or in particular citrate. This embodiment would enable rapid release of the oxybate by providing supplementing exchangeable anions in the stomach.

In another embodiment, the supplemental anions are provided by digestion of proteins administered with or as part of the formulation. The resulting amino acids are then available for exchange with the resin and can provide a more convenient means of providing a large amount of supplemental anion.

In yet another embodiment, the supplemental anions are provided by digestion of a triglyceride administered with the formulation. When the triglyceride empties into the small intestine, lipolysis will generate anions available for exchange. In general, triglycerides of short-chain fatty acids (such as triacetin or tributyrin) can provide better oxybate release than medium- or long-chain triglycerides, because the binding affinity of the resulting anions are higher due to their pKa and size. Triglycerides with at least one short-chain fatty acid component are also suitable, particularly pharmaceutically acceptable short-chain triglycerides such as triacetin.

If the resinate particles are film-coated, then supplemental anions can be provided as separate coated particles, such that the supplemental anion is available when needed. The supplemental anion can be selected such that it is not absorbed rapidly yet has an affinity for the resinate that is much higher than that of oxybate. It can be particularly useful to target or enhance release of the supplemental anion in the ileum where chloride secretory deficit may be most pronounced, since absorption of organic acids might be considerably less in that location. Citric acid, glycine, and mesalazine (5-aminosalicylic acid) are examples of suitable supplemental anions. A non-limiting list of other suitable anions (or conjugate acids) includes pharmaceutically acceptable salts selected from the group consisting of chlorides, acetates, lactates, bicarbonates, sulfates, citrates, tartrates, malates, maleates, malonates, glutarates, succinates, fumarates, aspartates, glutamates, and combinations thereof.

These supplemental anions can be coadministered with the oxybate compositions of the present invention, for example within about an hour (before or after) of administering the drug resinate (e.g., oxybate resinate) compositions of the present invention, or simultaneously therewith. The amount of such supplemental anions can range from about

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20 to about 200 mmoles, including about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, about 120, about 125, about 130, about 135, about 140, about 145, about 150, about 155, about 160, about 165, about 170, about 175, about 180, about 185, about 190, about 195, or about 200 mmoles, inclusive of all values and ranges therebetween. The supplemental anions can themselves be capable of anion exchange directly upon contact with the drug resinate (e.g., exchanging with the oxybate of the oxybate resinate), or can be “pro-anions”—that is, form anions upon biotransformation after administration to the patient. Non-limiting examples of such “pro-anions” are those described herein, such as triglycerides or proteins. The amount of such “pro-anions” suitable for use in treating patients according to the present invention are amounts that produce between about 20 and about 200 mmoles of anions, as described hereinabove.

If sustained release is desired, then extending gastric emptying can somewhat compensate for deficiencies in the jejunum and, particularly, the ileum. Reliably extending gastric emptying in the fasted state is very challenging. Although some investigators have found that administration of resinate particles can result in mucoadhesion, the unusually high molar doses of GHB of the resinate compositions of the present invention, approximately 100 mEq, will effectively cover the entire surface of the stomach many times over. Thus, observations made with conventional resinate formulations would not apply to GHB resinates. Therefore, a more effective means of promoting gastric retention would be administration of the compositions of the present invention with food or caloric liquid.

The oxybate compositions of the present invention, for example oxybate resinate compositions, provide therapeutically effective levels of oxybate over a period of at least about 3 to about 8 hours. In some embodiments, the composition can be considered to comprise a single population of resinate beads, wherein at least a portion of the resinate beads releases the oxybate quickly upon administration (essentially upon contacting physiologically produced anions such as chloride), and a remaining portion of the resinate beads releases oxybate more slowly, either controlled by the physiological rate of production of anions such as chloride, or by modification of the release characteristics of the resinate beads themselves (e.g., by providing a diffusion controlling coating, by control of bead diameter, or crosslinking density, or other method as described herein). If the compositions of the present invention comprise two or more distinct bead populations (distinguished by their oxybate release characteristics), the rapid (or immediate) release population provides therapeutically effective levels of oxybate for up to about 3 hours (including 1 or 2 hours) after administration, and the other population(s) provide therapeutically effective levels of oxybate for about 3 to about 8 hours (including 3, 4, 5, 6, 7, or 8 hours) after administration.

Xyrem for its approved indications is effective at between 6 g and 9 g administered twice nightly in equal amounts about 4 hours apart. A sustained release equivalent may require a matching AUC as compared to 9 g Xyrem. As disclosed in US2012076865, the overall relative bioavailability of an appropriately-timed sustained release would have at most about 75% relative to Xyrem. Therefore, about 12-13 grams of sodium oxybate would be required, or about 100 mMols.

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Suitable blood levels of oxybate are at least about 10 mg/L, ranging up to about 70 mg/L, maintained over a period of about 5-8 hours as described herein. For example suitable blood levels of oxybate can be about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, or about 70 mg/L, inclusive of all ranges therebetween.

The following examples are included to demonstrate particular embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute particularly suitable modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

All documents cited herein, including patents, patent publications, and non-patent publications are herein incorporated by reference in their entirety for all purposes.

EXAMPLES

Example 1

A gel-type Type 1 strong base anion exchange resin, Dowex 1X2 (Dow Chemical), 100-200 mesh was loaded with GHB as follows. Calcium oxybate was loaded onto resin in a batch equilibration by combining 10 mL of 4 M calcium oxybate solution (approximately 490 mg/mL), 31.7 mL of de-ionized water, and 20.27 g of Dowex 1X2 wet resin as chloride form with 2% crosslinking. After mixing for 2 hours, the resin was filtered under mild vacuum using a Buchner funnel. It was then washed with 700 mL of de-ionized water in approximately 100-150 mL aliquots to remove any free oxybate. The wet beads were then dried in a 60° C. oven for 3.5 hours, and finally sized through a 36-mesh screen. The resinate beads were assayed by suspending 1.5 g of resinate in 12.5 g of 1 M calcium chloride and allowing them to equilibrate overnight at room temperature. The solution was analyzed by HPLC, and the measured oxybate released from the beads was 1.09 mEq per gram of dry resinate. The calculated loading efficiency was 1.14 mEq/gram dry resin, or 33% of the theoretical exchange capacity of the resin.

Example 2

GHB resinate beads were prepared by contacting GBL with another Type 1 strong base anion exchange resin (Amberlite IRN78, Dow Chemical) having a median particle size of about 0.63 mm, as the hydroxide form with 8% crosslinking. Batch B1 was prepared with a 2:1 molar ratio of GBL to hydroxide-bearing sites by suspending 26.78 g of wet resin in 41.2 g of de-ionized water. While stirring, 8.28 g of GBL was added, and the reaction was monitored by HPLC analysis of unreacted GBL. The reaction was largely complete after 30 minutes. After 90 minutes, the resin was filtered under mild vacuum, rinsed with de-ionized water to remove unreacted GBL, and then placed in a 60° C. oven overnight to dry.

Batch B2 was prepared by reacting GBL in only 16% molar excess over hydroxide-bearing sites on the same resin. 2.6 g of GBL was added to 20 g of wet resin (as supplied) while stirring by hand with a spatula. About 5.3 g of

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additional water was added to facilitate blending. After about 1 hour, the mass was placed in the 60° C. oven overnight to complete the reaction, if necessary. The beads were then rinsed with de-ionized water (70 mL), filtered under mild vacuum, and transferred to the 60° C. oven for drying over 3 days.

The two batches were analyzed for oxybate content by first suspending 1.0 g of resinate in 20 mL of 2 M NaCl for 2 hours with stirring. 10 mL of the resulting solution was then titrated with 1 N HCl and the results were compared with a blank of 10 mL of 2 N NaCl. The initial pH values of B1 and B2 were 7.0 and 8.3, respectively, thus indicating that very little, if any, unreacted hydroxide was present in the resinate product. The oxybate titration indicated that GHB loadings of 4.2 and 4.3 mEq/g dry resin for B1 and B2, respectively. The result further indicates that complete reaction occurred, as the theoretical capacity of the resin is approximately 4 mEq/g.

Example 3

A larger batch of GHB resinate beads are prepared by reacting GBL with Amberlite IRN78 under conditions represented by Batch B2. GBL (36.9 g) is slowly added to a slurry of wet resin (Amberlite IRN78, 279 g) and water (about 200 g). The reaction is allowed to proceed for at least 1 hour at room temperature, with stirring. The product is vacuum filtered, then rinsed with several volumes of de-ionized water. The wet product is then placed in a 40° C. oven to dry overnight. 2.1 g of dried GHB resinate beads are then administered to each of 6 beagle dogs, fasted and weighing approximately 10-12 kg, by oral gavage. Blood is sampled at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 10 h for determination of plasma GHB content.

Example 4

Amberlite IRN78, a hydroxide form Type 1 anion exchange resin, is charged to a vessel and contacted with a 1M solution of sodium oxybate in a 2:1 stoichiometry to resin equivalents. After about 2 hours of equilibration, the mixture of sodium oxybate and sodium hydroxide is filtered from the resulting resinate. A sample of the solution is titrated to determine sodium hydroxide content, and then an equivalent amount of calcium oxybate is charged to the solution to precipitate calcium hydroxide. The calcium hydroxide is filtered from the solution of sodium oxybate, and the recovered sodium oxybate solution is returned to the equilibration tank and contacted with the wet resinate for 2 hours. The resinate is then filtered, and filtrate is recovered. The recovered filtrate is processed with calcium oxybate as in the first step, and set aside for future use. The resinate product is washed with several volumes of de-ionized water, and then dried.

Example 5

Cholestyramine (chloride form) is charged to a vessel and contacted with 1M sodium bicarbonate in a 2:1 stoichiometry (bicarbonate to resin). Five cycles of batch equilibration (2 h each) are conducted. The solutions in each cycle are not recycled, and resinate is rinsed with 2 volumes of de-ionized water between each cycle.

The wet, bicarbonate-exchanged resin is then contacted with 1M sodium oxybate in a single equilibration step in a 2:1 molar ratio of oxybate to resin. After 2 h, the resinate is filtered, and filtrate collected. Separately, the GHB-resinate

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is then washed with several volumes of de-ionized water. A sample of the first filtrate is titrated for bicarbonate content, and then a stoichiometric amount of calcium oxybate is added to the batch filtrate. The precipitated calcium carbonate is removed by filtration of the suspension, and the sodium oxybate solution is recovered and stored for future use.

Example 6

The above examples can involve difficult separation steps, as precipitated calcium carbonate is a thick slurry of fine particles at the concentrations used. In this example, filtration is avoided by use of a reaction in which the byproduct forms carbon dioxide rather than a precipitate.

The wet, bicarbonate-exchanged resin of Example 5 is contacted with 1M sodium oxybate in a single equilibration step in a 2:1 molar ratio of oxybate to resin. After 2 h, the resinate is filtered, and filtrate collected. Oxybate is recovered and bicarbonate is removed from the filtrate by addition of a stoichiometric amount of sodium hydroxide such that the bicarbonate is converted to carbonate by the reaction: $\text{NaOH} + \text{NaHCO}_3 \rightarrow \text{Na}_2\text{CO}_3 + \text{H}_2\text{O}$. The pH drives this reaction to completion.

Next, GBL is added at a 1:1 stoichiometry. Sodium carbonate reacts with the GBL with the evolution of carbon dioxide gas, which drives the reaction to completion: $2 \text{GBL} + \text{Na}_2\text{CO}_3 + \text{H}_2\text{O} \rightarrow 2 \text{Na-GHB} + \text{CO}_2(\text{g})$. Optionally, a small excess of sodium hydroxide can be added to avoid conversion to bicarbonate during the reaction. This overall process avoids the filtration of carbonate, recovers all the sodium as unexchanged sodium oxybate, and replaces the exchanged sodium oxybate with new oxybate derived from GBL.

Example 7

Soy protein isolate is compressed into oblong or oval tablets of approximately 1000 mg, using compression aids such as fillers, microcrystalline cellulose, and lubricants as required. The tablets are enteric coated separately with two different polymers to achieve dissolution and release of the soy protein isolate in the jejunum and ileum. One batch is coated with Eudragit L30D-55 (jejunum-targeted), and the other is coated with Eudragit L100 (ileum-targeted). At least two of each kind of tablets are taken with one dose of GHB-resinate (35.7 mEq of resinate equivalent to 4.5 g oxybate) in a glass of water. This provides at least 36 mEq of amino acid content, as the protein is hydrolyzed. By releasing the protein in the small intestine rather than stomach, complete and rapid digestion is avoided. Instead, the protein is digested to amino acids more gradually as it transits the small intestine and as the tablet disintegrates. The amino acids are therefore available to facilitate exchange of the GHB-resinate taken concomitantly.

We claim:

1. A method of treating narcolepsy in a patient in need thereof, the method comprising:

administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:

opening a sachet containing a solid oxybate formulation, mixing the formulation with water, and

orally administering the mixture to the patient, wherein the oxybate formulation comprises an immediate release component and a controlled release component.

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2. The method of claim 1, wherein the orally administering occurs at night.

3. The method of claim 1, wherein the oxybate formulation is mixed with water immediately prior to administration.

4. The method of claim 1, wherein the oxybate is administered with food.

5. The method of claim 1, wherein the administering promotes the patient to sleep for 6 to 8 hours.

6. The method of claim 1, wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.

7. The method of claim 1, wherein the mixture is a suspension.

8. The method of claim 1, wherein the oxybate formulation further comprises an acid.

9. The method of claim 8, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

10. A method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof, the method comprising:

administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:

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opening a sachet containing a solid oxybate formulation, mixing the formulation with water, and

orally administering the mixture to the patient, wherein the oxybate formulation comprises an immediate release component and a controlled release component.

11. The method of claim 10, wherein the orally administering occurs at night.

12. The method of claim 10, wherein the oxybate formulation is mixed with water immediately prior to administration.

13. The method of claim 10, wherein the oxybate is administered with food.

14. The method of claim 10, wherein the administering promotes the patient to sleep for 6 to 8 hours.

15. The method of claim 10, wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.

16. The method of claim 10, wherein the mixture is a suspension.

17. The method of claim 16, wherein the oxybate formulation further comprises an acid.

18. The method of claim 17, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

* * * * *

EXHIBIT 7

Attorney Docket No. JAZZ-025/03US 306882-2411

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor: Clark ALLPHIN. Confirmation No.: 6759
Serial No.: 17/118,041 Group Art Unit: 1617
Filed: December 10, 2020 Examiner: Yanzhi ZHANG
FOR: **GHF FORMULATION AND METHOD FOR ITS MANUFACTURE**

VIA EFS-Web

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE UNDER 37 C.F.R. §1.111

This paper is in response to non-final Office Action dated February 24, 2021. Thus, this response is timely filed by May 24, 2021.

Applicant requests reconsideration in view of the following amendments and remarks.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: CLARK ALLPHIN, et al. Confirmation No.: 6759

Serial No.: 17/118,041 Group Art Unit: 1617

Filed: December 10, 2020 Examiner: ZHANG, YANZHI C

FOR: **GHB FORMULATION AND METHOD FOR ITS MANUFACTURE**

DECLARATION OF CLARK ALLPHIN UNDER 37 C.F.R. §1.132

1. I am an inventor of the above-identified application, and I am currently employed by Jazz Pharmaceuticals, Inc. as the Executive Director of Process and Product Science, New Product and Technology Integration. I have twenty-five years of development experience in the field of pharmaceutical formulations.¹ I received a Bachelor of Science degree in Chemical Engineering from the University of California, Berkeley.

2. I am familiar with the above-identified application and reviewed the Office Action dated February 24, 2021, the references cited therein and the Applicant Initiated Interview Summary dated April 30, 2021.

3. It is my understanding that the Examiner believes the presently claimed methods are obvious over Alshaikh et al, Journal of Clinical Sleep Medicine, Vol. 8, No. 4, 2012 ("*Alshaikh*"); Luhn, O., Pharmaceutical Technology Europe, Volume 23, Issue 1, January 7, 2011 ("*Luhn*"); Oral rehydration salts, Neonatal and Pediatric Pharmacists Group, July 25, 2013 ("*NPPG*"); Borgen et al, Journal of Clinical Pharmacology, 2003; vol. 43, pp. 59-65 ("*Borgen*"); and U.S. Patent No. 8,591,922 B1 ("*Allphin*"). I respectfully disagree with the Examiner's conclusion.

¹ I have 35 years' experience as chemical engineer, 25 years in the pharmaceutical industry starting in oral product formulation for sustained release products.

4. As background to the claimed invention, oxybate's physical and pharmacokinetic characteristics present unique challenges when developing oxybate formulations and effective oxybate dosing regimens. Oxybate salts are known to be hygroscopic, *i.e.*, the monovalent salts readily and rapidly absorb moisture from the surrounding atmosphere, and in fact some of them deliquesce. Furthermore, oxybate is rapidly cleared from a patient's bloodstream after administration (*i.e.*, oxybate has a short *in vivo* half-life) so multiple daily administrations are required to maintain therapeutically effective oxybate blood concentrations.²

5. In fact, when the present application was filed in 2015, the only FDA-approved oxybate-containing drug product was Xyrem®. Xyrem® was approved in 2002 to treat cataplexy and excessive daytime sleepiness in narcolepsy patients.³ Xyrem® is a liquid, oral solution of sodium oxybate, and the product label instructions require twice-a-night administration for therapeutic effectiveness.

6. With this background, I do not think a skilled artisan would have considered the claimed methods to be obvious over the cited references. The presently-claimed inventions are directed to methods of treating oxybate-treatable conditions⁴ by administering to a patient a single daily dose of a solid oxybate formulation that is dispensed from a sachet packaging and mixed with water prior to administration.

7. No cited reference describes or suggests administering a solid oxybate formulation in a sachet dosage form let alone according to a once-a-day administration schedule. *Alshaikh*, which I understand is the primary reference cited by the Examiner, merely summarizes clinical studies that were conducted using liquid oxybate formulations and where the oxybate was dosed twice-a-day. *Alshaikh* does not suggest using a sachet dosage form and, in fact, does not even describe the liquid formulations that were tested in the summarized clinical studies.

8. *Luhn* does not relate to oxybate at all. Instead, *Luhn* generally asserts that pharmaceutical sachets may be useful in certain circumstances, such as when existing dosage forms have poor

² Specification at paragraph (013)

³ Specification at paragraph (003).

⁴ Claim 10 is directed to the treatment of narcolepsy. Claim 19 is directed to the treatment of cataplexy or excessive daytime sleepiness associate with narcolepsy. Like claim 1, claims 10 and 19 require a solid dosage form (*i.e.*, solid oxybate formulation packaged in a sachet) and effectively treat the conditions using a single daily oxybate dose.

patient compliance. Since the cited art does not teach any such issues with the existing liquid oxybate formulations, I do not consider *Luhn* to be particularly relevant to the specific challenges faced when developing an oxybate formulation. Furthermore, according to *Luhn*, sachets are common in the confectionary field but less so in pharmaceutical industry because of regulatory and manufacturing challenges. Regulatory and manufacturing challenges are often of primary concern when developing a pharmaceutical product. In my experience, pharmaceutical developers prefer to rely on known, proven technologies for product development. *Luhn* acknowledges that sachets are not a widely used pharmaceutical technology. Because *Luhn* only provides general guidance related to sachet formulations and acknowledges that sachets are not a generally-adopted pharmaceutical technology, it is my opinion that a skilled person would not be motivated by *Luhn* to prepare sachet oxybate formulations, especially provided the hygroscopic nature of oxybate salts (see above).

9. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 20 May 2021



Clark Allphin

Electronic Patent Application Fee Transmittal				
Application Number:	17118041			
Filing Date:	10-Dec-2020			
Title of Invention:	GHB FORMULATION AND METHOD FOR ITS MANUFACTURE			
First Named Inventor/Applicant Name:	Clark ALLPHIN			
Filer:	Jason Conley Valentine/Kommala Keovongphet			
Attorney Docket Number:	JAZZ-025/03US 306882-2411			
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	3	100	300
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				300

Electronic Acknowledgement Receipt

EFS ID:	42780173
Application Number:	17118041
International Application Number:	
Confirmation Number:	6759
Title of Invention:	GHB FORMULATION AND METHOD FOR ITS MANUFACTURE
First Named Inventor/Applicant Name:	Clark ALLPHIN
Customer Number:	128521
Filer:	Jason Conley Valentine/Kommala Keovongphet
Filer Authorized By:	Jason Conley Valentine
Attorney Docket Number:	JAZZ-025/03US 306882-2411
Receipt Date:	20-MAY-2021
Filing Date:	10-DEC-2020
Time Stamp:	17:51:41
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$300
RAM confirmation Number	E20215JH51544289
Deposit Account	
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1		JAZZ-025_03US-Response_Non-Final_OA.pdf	145008	yes	12
			00680a20ae4196109b055450c91029b8b7a95646		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Applicant Arguments/Remarks Made in an Amendment		7	12	
	Claims		2	6	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
Warnings:					
Information:					
2	Affidavit-traversing rejectns or objectns rule 132	JAZZ-025_03US-Allphin_Declaration_05_20_2021_signed.pdf	453272	no	3
			b6163cf109234dcda05729c483d152733d2c4b86		
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30615	no	2
			589b91b343ab1eab63fc967fb7f7df458a34d321		
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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Attorney Docket No. JAZZ-025/03US 306882-2411
US Application No. 17/118,041; Filed: December 10, 2020

REMARKS

I. Status of Claims

Claims 1, 6, 10, 15, 19 and 24 are amended. Dependent claims 28-30 are new. After entry of these amendments, claims 1-30 are pending.

Claims 1, 10 and 19 are amended to specify that the claim-recited sachets contain a solid oxybate formulation. Claims 6, 15 and 24 are amended to correct a typographical mistake.

Claims 28, 29 and 30 depend from claims 1, 10 and 19, respectively, and further specify that the administered solid oxybate formulations contain an immediate release component and a controlled release component. Support for the claim amendments can be found throughout the application as originally filed, including paragraphs (0027) and (0076).

No new matter is added by these amendments.

II. Interview Summary

Applicant thanks Examiner Zhang for the courtesies extended during the Interview conducted on April 26, 2021. Applicant generally discussed the issues raised by the present office action and explained that they disagree with the Examiner's position that the cited prior art renders Applicant's claimed subject matter obvious.

III. Claim Rejections under 35 U.S.C. § 103

Claims 1-27 are rejected under 35 U.S.C. §103 as allegedly obvious over combinations of Alshaikh et al, Journal of Clinical Sleep Medicine, Vol. 8, No. 4, 2012 ("*Alshaikh*"); Luhn, O., Pharmaceutical Technology Europe, Volume 23, Issue 1, January 7, 2011 ("*Luhn*"); Oral rehydration salts, Neonatal and Pediatric Pharmacists Group, July 25, 2013 ("*NPPG*"); Borgen et

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al, Journal of Clinical Pharmacology, 2003; vol. 43, pp. 59-65 (“*Borgen*”); and U.S. Patent No. 8,591,922 B1 (“*Allphin*”). The Applicants traverse.

a. Claimed subject matter

The presently claimed subject matter is directed to methods of treating oxybate-treatable conditions¹ by administering to a patient a single daily dose of a solid oxybate formulation. The solid oxybate formulation is dispensed from a sachet and mixed with water prior to the administration.

b) The Examiner has not established a *prima facie* case of obviousness

To summarize, the Examiner cites *Luhn* for the use of a sachet and *Alshaikh* to administer GHB according to instructions provided by *NPPG*.² Applicant traverses.

The Examiner has not articulated a legally sufficient reason to combine the cited references to arrive at the presently claimed invention

Neither *Alshaikh*, *Luhn*, *Borgen* nor *Allphin*, alone or in combination, teach or suggest the claimed method of administering a solid oxybate formulation using a sachet, let alone the sachet’s once daily administration to treat an oxybate-treatable condition. As discussed below, and in the *Allphin Declaration*, a person of ordinary skill in the art (“POSA”) would not combine the cited references in such a manner to arrive at the claimed invention containing all the recited elements.³

¹ Claim 10 is directed to the treatment of narcolepsy. Claim 19 is directed to the treatment of cataplexy or excessive daytime sleepiness associate with narcolepsy. Claims 10 and 19 require a solid dosage form (i.e., solid oxybate formulation packaged in a sachet) and effectively treat the recited conditions using a single daily oxybate dose.

² Office Action at pages 3-10.

³ Declaration of Clark Allphin under 37 C.F.R. § 1.132 (submitted herewith, “*Allphin Declaration*”) at paragraphs 4-8.

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As stated in *In re Kubin*, obviousness should not be found when one “merely throws metaphorical darts at a board filled with combinatorial prior art possibilities. . . .”⁴ The Examiner cannot pick and choose elements of a reference and piece them together without a particular motivation for doing so:

[A] rejection cannot be predicated on the mere identification in [the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.⁵

As a first matter, a skilled artisan seeking to prepare an oxybate formulation would not look to *Luhn* (which the Examiner relies on as teaching sachet formulation) for guidance for the simple reason that the reference is not addressed to the many particular challenges faced when developing an oxybate formulation. As explained in the *Allphin Declaration*, *Luhn* does not relate to oxybate at all, which is particularly relevant since oxybate salts are extremely hygroscopic solids (i.e., they “readily and rapidly absorb moisture from the surrounding environment”).⁶ Extremely hygroscopic active pharmaceutical ingredients are difficult to formulate in solid pharmaceutical dosage forms (as recited in the claims) because, for example, they may deliquesce.⁷ *Luhn* does not in any way address the issue of formulating hygroscopic active ingredients and, as such, a POSA would not look to *Luhn* for guidance when preparing solid oxybate formulations, or for the use of oxybate in a sachet.⁸

As acknowledged by the Examiner, *Alshaikh* does not describe a sachet dosage form or its method of administration.⁹ Instead, *Alshaikh* merely summarizes clinical studies of oxybate

⁴ *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

⁵ *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000) (emphasis added).

⁶ *Allphin Declaration* at paragraph 4.

⁷ *Allphin Declaration* at paragraph 4.

⁸ *Allphin Declaration* at paragraph 8. Furthermore, *Luhn* itself indicates that sachet formulations are not widely used in the pharmaceutical industry because of manufacturing and regulatory challenges. *Luhn* at page 2/6.

⁹ Office Action at page 5.

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without discussing the pharmaceutical form administered to patients. As Mr. Allphin points out, the studies summarized in *Alshaikh* utilized oral solutions of oxybate.¹⁰ Furthermore, at the time the present application was filed, the only FDA-approved oxybate product was Xyrem®, an oral, liquid solution of sodium oxybate that was approved in 2002.¹¹ If anything, then, the prior art as a whole teaches against using a solid oxybate formulation in a sachet, as required by the present claims.

Here, the Examiner asserts that *Luhn* teaches that sachet formulations may be beneficial in certain circumstances, such as when the existing formulations have poor patient compliance.¹² *Luhn* is an unsupported opinion article that does not discuss the utility of a sachet with respect to any particular drug, or class of drug. In fact, *Luhn* itself arguably teaches away from the claimed method because it recites many reasons that the pharmaceutical industry would likely not adopt the use of sachets, such as it is a non-established technology, the lack of regulatory experience and lack of the necessary manufacturing equipment.¹³ *Luhn* further explains that the use of sachets is a crossover from the confectionary field to pharmaceutical field, which “used to be absolutely contradictory.”¹⁴ Even *Luhn*’s support for applying ideas from the confectionary industry to pharmaceuticals is highly qualified¹⁵ These statements substantially narrow *Luhn*’s teachings and a fair reading of *Luhn* cannot be that it recommends using sachets for all pharmaceutical ingredients, especially those that are extremely hygroscopic, like oxybate.

Simply put, the Examiner has not provided a legally-sufficient justification why a POSA would apply the qualified opinions expressed by *Luhn* to oxybate to arrive at the presently claimed

¹⁰ *Allphin Declaration* at paragraph 7.

¹¹ Specification at paragraph (003) and *Allphin Declaration* at paragraph 5.

¹² Office Action at pages 5-6.

¹³ *Luhn* at page 2/6.

¹⁴ *Luhn* at page 3/6.

¹⁵ *Luhn* states that the adoption of confectionary methods in pharmaceuticals “could possibly be done with sachets.” *Luhn* at page 3/6 (underline added).

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subject matter (e.g., not established that there is poor patient compliance with the Xyrem[®] product to justify the change to a sachet). Importantly, as explained in the *Allphin Declaration*, there are specific reasons why a POSA would not combine *Luhn*'s sachets with oxybate (e.g., oxybate salts are highly hygroscopic,¹⁶ *Luhn*'s acknowledgment that sachets are not a generally-adopted pharmaceutical technology and pharmaceutical developers' preference to use proven technologies when developing products¹⁷). *Luhn* provides no specific teaching to the contrary.

Thus, the Examiner's motivation is insufficient as a matter of law to combine *Luhn* with the other cited references in the manner suggested and, as such, the claims are not obvious over the cited references.

Examiner's Rejection Does Not Address All the Claim Elements

The Examiner's rejection is deficient as a matter of law because it does not provide a rationale to administer a single daily dose of a solid oxybate formulation to the patient from a sachet.¹⁸

This deficiency is particularly relevant because, when the present application was filed, it was understood in the art that oxybate required twice-daily administration to be therapeutically effective. For example, the label instructions for Xyrem[®], the only then-approved oxybate-containing product, required twice-daily administration,¹⁹ and the oxybate efficacy trials summarized in *Alshaikh* (and relied on by the Examiner) all utilized twice daily oxybate administration.²⁰ Therefore, none of the cited references suggests the claim-recited single daily

¹⁶ *Allphin Declaration* at paragraph 4.

¹⁷ *Allphin Declaration* at paragraph 8.

¹⁸ MPEP 2140.03.

¹⁹ *Allphin Declaration* at paragraphs 4-5.

²⁰ *Allphin Declaration* at paragraphs 7.

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administration of a solid oxybate formulation dispensed from a sachet to treat an oxybate-treatable condition.

In contrast, the presently-claimed methods provide therapeutic effectiveness through once-daily administration by, for example, administering solid oxybate compositions packaged in a sachet that contain both immediate and extended release components.²¹

CONCLUSION

In view of the foregoing, Applicants respectfully submit that this application is in condition for allowance and request favorable action thereon. They assert that the cited references do not show or suggest the presently claimed subject matter. For example, the *Luhn* reference teaches away from the combination and none of the other references provide the lacking elements for the reasons suggested above. The Examiner is invited to contact the undersigned if any additional information is required.

Dated: May 20, 2021

COOLEY LLP

ATTN: Patent Group

1299 Pennsylvania Avenue NW, Suite 700
Washington, DC 20004

Tel: (202) 728-7157

Fax: (202) 842-7899

Respectfully submitted,
COOLEY LLP

By: / Jason C. Valentine /
Jason C. Valentine
Reg. No. 70,211

²¹ See new dependent claims 28, 29 and 30.

IN THE CLAIMS:

Set forth below in ascending order, with status identifiers, is a complete listing of all claims currently under examination. Changes to any amended claims are indicated by [[double brackets]], ~~strike through~~ and/or underlining. This listing also reflects any cancellation and/or addition of claims.

1. (Currently amended) A method of treating a disease or condition treatable with oxybate in a patient in need thereof, the method comprising:

administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:

opening a sachet containing ~~an~~ a solid oxybate formulation,

mixing the formulation with water, and

orally administering the mixture to the patient.
2. (Previously presented) The method of claim 1, wherein the orally administering occurs at night.
3. (Previously presented) The method of claim 1, wherein the oxybate formulation is mixed with water immediately prior to administration.

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4. (Previously presented) The method of claim 1, wherein the oxybate is administered with food.
5. (Previously presented) The method of claim 1, wherein the administering promotes the patient to sleep for 6 to 8 hours.
6. (Currently amended) The method of claim 1, wherein the amount of oxybate administered to the ~~human~~ patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.
7. (Previously presented) The method of claim 1, wherein the mixture is a suspension.
8. (Previously presented) The method of claim 1, wherein the oxybate formulation further comprises an acid.
9. (Previously presented) The method of claim 8, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.
10. (Currently amended) A method of treating narcolepsy in a patient in need thereof, the method comprising:

administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:

opening a sachet containing ~~an~~ a solid oxybate formulation,

mixing the formulation with water, and

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orally administering the mixture to the patient.

11. (Previously presented) The method of claim 10, wherein the orally administering occurs at night.
12. (Previously presented) The method of claim 10, wherein the oxybate formulation is mixed with water immediately prior to administration.
13. (Previously presented) The method of claim 10, wherein the oxybate is administered with food.
14. (Previously presented) The method of claim 10, wherein the administering promotes the patient to sleep for 6 to 8 hours.
15. (Currently amended) The method of claim 10, wherein the amount of oxybate administered to the ~~human~~ patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.
16. (Previously presented) The method of claim 10, wherein the mixture is a suspension.
17. (Previously presented) The method of claim 10, wherein the oxybate formulation further comprises an acid.
18. (Previously presented) The method of claim 17, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

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19. (Currently amended) A method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof, the method comprising:
- administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:
- opening a sachet containing ~~an~~ a solid oxybate formulation,
- mixing the formulation with water, and
- orally administering the mixture to the patient.
20. (Previously presented) The method of claim 19, wherein the orally administering occurs at night.
21. (Previously presented) The method of claim 19, wherein the oxybate formulation is mixed with water immediately prior to administration.
22. (Previously presented) The method of claim 19, wherein the oxybate is administered with food.
23. (Previously presented) The method of claim 19, wherein the administering promotes the patient to sleep for 6 to 8 hours.
24. (Currently amended) The method of claim 19, wherein the amount of oxybate administered to the ~~human~~ patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.

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25. (Previously presented) The method of claim 19, wherein the mixture is a suspension.
26. (Previously presented) The method of claim 25, wherein the oxybate formulation further comprises an acid.
27. (Previously presented) The method of claim 26, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.
28. (New) The method of claim 1, wherein the oxybate formulation comprises an immediate release component and a controlled release component.
29. (New) The method of claim 10, wherein the oxybate formulation comprises an immediate release component and a controlled release component.
30. (New) The method of claim 19, wherein the oxybate formulation comprises an immediate release component and a controlled release component.

PATENT APPLICATION FEE DETERMINATION RECORD				Application or Docket Number 17/118,041		Filing Date 12/10/2020		<input type="checkbox"/> To be Mailed			
Substitute for Form PTO-875											
ENTITY: <input checked="" type="checkbox"/> LARGE <input type="checkbox"/> SMALL <input type="checkbox"/> MICRO											
APPLICATION AS FILED - PART I											
		(Column 1)		(Column 2)							
FOR		NUMBER FILED		NUMBER EXTRA		RATE (\$)		FEE (\$)			
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A		N/A		N/A					
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A		N/A		N/A					
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A		N/A		N/A					
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 = *				x \$100 =					
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 = *				x \$480 =					
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).									
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))											
* If the difference in column 1 is less than zero, enter "0" in column 2.						TOTAL					
APPLICATION AS AMENDED - PART II											
		(Column 1)		(Column 2)		(Column 3)					
AMENDMENT	05/20/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 30	Minus	** 27	= 3			x \$100 =		300	
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0			x \$480 =		0	
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))										
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))										
								TOTAL ADD'L FEE		300	
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=			x \$0 =			
	Independent (37 CFR 1.16(h))	*	Minus	***	=			x \$0 =			
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))										
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))										
								TOTAL ADD'L FEE			
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.								LIE			
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".								/TERRY BRYANT/			
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EXHIBIT 8

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indicator chart

indicator chart *noun* COMPUT a graphical representation of the location and use of indicator flags within a program

indicator flag *noun* COMPUT a register or single bit that indicates the state of the processor and its registers, e.g. a carry or overflow

indicator light *noun* a light used to warn or indicate the condition of equipment

indicator species *noun* ENVIRON a species which is very sensitive to particular changes in the environment and can show that environmental changes are taking place

indigenous *adjective* ECOL native to a place ○ *There are six indigenous species of monkey on the island.* ○ *Bluebells are indigenous to the British Isles.*

indigo *noun* PLANTS a tropical plant of the pea family which is a source of blue dye. Genus: *Indigofera*.

indirect address *noun* COMPUT same as **relative address**

indirect addressing *noun* COMPUT a way of addressing data in which the first instruction refers to an address which contains a second address

indium *noun* CHEM ELEM a soft silvery metal, used in alloys, transistors and electroplating (NOTE: The chemical symbol is **In**; the atomic number is **49** and the atomic weight is **114.82**.)

indium phosphide *noun* CHEM a brittle metallic solid used in the manufacture of semiconductors, lasers and solar cells

individual *adjective* existing as a separate thing ○ *The hydraulic braking system consists of a master cylinder with individual brake cylinders at each wheel.* ○ *The individual workstations are all linked to the mainframe.* ■ *noun* BIOL a single organism or item considered as one rather than as a member of a group

individual variation *noun* the range of differences found between individuals within a population

indivisible *adjective* MATHS not capable of being divided by a given number without leaving a mathematical remainder

induce *verb* 1. to cause something to happen ○ *Unequal deposits on moving parts can induce severe vibration, especially on propellers and helicopter rotors.* 2. ELEC to generate an electrical current in a coil of wire by electromagnetic effects

induced drag *noun* AEROSP the part of total drag created by lift

COMMENT: Induced drag is created when high-pressure air below a wing rotates around the tip to the low-pressure area above and increases as airspeed decreases and angle of attack increases. The other basic type of drag is parasite drag.

induced failure *noun* the failure of a device due to external effects

induced interference *noun* ELEC electrical noise on a signal due to induced signals from nearby electromagnetic sources

inducer *noun* 1. BIOL, BIOCHEM a substance which changes the way in which an enzyme acts 2. GENETICS a substance which activates a structural gene within a cell

inductance *noun* ELEC a measure of the ability of a conductor to bring a voltage into itself when carrying an alternating current, e.g. during short times when the circuit is switched on or off ○ *At low frequencies, the rate of collapse of the magnetic field will be slow and the inductance will be low.*

induction *noun* 1. MECH ENG the process by which the fuel/air mixture is drawn into the cylinders of an internal combustion engine ○ *The four strokes of the engine are induction, compression, combustion and exhaust.* 2. ELEC the generation of an electrical current due to electromagnetic effects from a nearby source ○ *A transformer is a static device that changes the amplitude or phase of an alternating voltage or current by electro-magnetic induction.* 3. BIOL the process of changing the way in which an enzyme acts

induction coil *noun* ELEC ENG a transformer that produces an intermittent high-voltage current from a low-voltage source by means of several wire windings generally around a soft iron core

induction heating *noun* ELEC a process by which the temperature of a metal is increased by an alternating magnetic field which induces an electric current within it

induction motor *noun* ELEC ENG an electric motor in which interactions between alternating currents in its windings create a varying magnetic field and induce a rotor to turn

inductive *adjective* ELEC referring to the production of electrical current in a conductor by a change of magnetic field ○ *One*

projected to rise sharply. **3.** to make an image appear on a surface

projectile *adjective* **1.** moving forwards with force **2.** ZOOL able to push suddenly forward, as are the jaws of some fish or the mouthparts of a dragonfly larva ■ *noun* an object that is thrown or moves with force

projection *noun* **1.** a part that sticks out **2.** an estimate or assessment of something that will happen in the future **3.** the production of an image on a surface **4.** GEOG a technique for making a map

prokaryote *noun* BIOL a simple organism such as a bacterium whose DNA is not contained within a nucleus. Compare **eukaryote**

prokaryotic *adjective* BIOL referring to prokaryotes

prolactin *noun* BIOCHEM a hormone produced by the pituitary gland that stimulates milk production after childbirth

proline *noun* BIOCHEM an amino acid found in many proteins, especially collagen. Formula: $C_5H_9NO_2$.

PROLOG *noun* COMPUT a high-level programming language using logical operations for artificial intelligence and data retrieval applications. Full form **programming in logic**

prolong *verb* to increase the duration or time of something, sometimes unnecessarily ○ *to prolong the life of an engine*

prolonged *adjective* lasting for a long time ○ *prolonged drought*

PROM *COMPUT* **1.** same as **programmable memory** **2.** same as **programmable read-only memory**

promethium *noun* CHEM ELEM a radioactive metallic element used in phosphorescent paints and as an X-ray source (NOTE: The chemical symbol is **Pm**; the atomic number is **61** and the atomic weight is **145**.)

prominence *noun* ASTRON a visible stream of glowing gas that shoots out from the Sun, seen in the upper chromosphere and lower corona (NOTE: Prominences are visible at the rim of the Sun during an eclipse.)

promontory *noun* EARTH SCI an area of high land which projects into the sea

promote *verb* to encourage or enable something to take place ○ *Growth-promoting hormones are used to increase the weight of beef cattle.*

promoter *noun* **1.** CHEM a substance that increases the activity of a catalyst **2.** GENETICS a gene that controls the expression of structural genes. Also called **promoter gene**

promoter gene *noun* GENETICS same as **promoter** **2**

promotion *noun* the activity of encouraging or enabling something to take place ○ *the promotion of recycling schemes*

prompt *noun* COMPUT a message or character displayed to remind the user that an input is expected ○ *The prompt READY indicates that the system is available to receive instructions.*

proof *noun* MATHS the series of logical stages used to establish whether a mathematical or philosophical proposition is valid

propagate *verb* **1.** BIOL to reproduce **2.** AGRIC to produce new plants by a technique such as taking cuttings, grafting, budding or layering ○ *fuschias propagated from cuttings* **3.** COMPUT to travel or spread

propagated error *noun* COMPUT one error in a process that has affected later operations

propagation *noun* **1.** AGRIC the production of new plants ○ *propagation by runners* ○ **vegetative propagation** **2.** ELEC the transmission of radio waves ○ *The speed of propagation of radio waves is slower over land than sea.*

propagation delay *noun* COMPUT **1.** the time taken for an output to appear in a logic gate after the input is applied **2.** the time taken for a data bit to travel over a network from the source to the destination

propagator *noun* BOT a closed but transparent container in which seed can be sown or cuttings grown in a moist, warm atmosphere

propanal *noun* CHEM a colourless liquid aldehyde. Formula: C_2H_5CHO .

propane *noun* INDUST a gas found in petroleum, which is sold commercially in liquid form under pressure as LPG

propel *verb* to cause something to move, especially at speed ○ *Fronts are propelled by the wind behind them.*

propellant *noun* INDUST **1.** a gas used in an aerosol can to make the spray come out **2.** a substance used to make something move forwards, e.g. rocket fuel

EXHIBIT 9

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Managing Editors Margaret Deuter

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Speaking Tutor Mark Hancock

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in-dis-able /ɪnˈdɪzəbəl/ *adj.* (formal) unable to do sth because you are ill/sick, or for a reason you do not want to give **SYN** **unwell** 2 [not before noun] ~ to do sth not willing to do sth

in-dis-posit-ion /ɪnˈdɪspəzɪʃn/ *noun* [C, U] (formal) a slight illness that makes you unable to do sth

in-dis-put-able /ɪnˈdɪspjuːtəbəl/ *adj.* that is true and cannot be disagreed with or denied **SYN** **undeniable**: indisputable evidence ◊ an indisputable fact ◊ It is indisputable that the crime rate has been rising. ◊ **COMPARE** **DISPUTABLE** ► **in-dis-put-ably** *adv.*: This painting is indisputably one of his finest works.

in-dis-sol-uble /ɪnˈdɪsɒljəbəl/ *adj.* (formal) (of a relationship) that cannot be ended: an indissoluble friendship ► **in-dis-sol-ubly** /ɪnˈdɪsɒljəbəl/ *adv.*: indissolubly linked

in-dis-tinct **AWL** /ɪnˈdɪstɪŋkt/ *adj.* that cannot be seen, heard or remembered clearly **SYN** **vague**, **hazy** ► **in-dis-tinct-ly** *adv.*

in-dis-tin-guish-able /ɪnˈdɪstɪŋɡwɪʃəbəl/ *adj.* 1 ~ (from sth) if two things are indistinguishable, or one is indistinguishable from the other, it is impossible to see any differences between them: The male of the species is almost indistinguishable from the female. 2 not clear; not able to be clearly identified: His words were indistinguishable.

in-dium /ɪnˈdiəm/ *noun* [U] (symb. **ln**) a chemical element. Indium is a soft silver-white metal.

in-di-vid-ual **AWL** /ɪnˈdɪvɪdʒuəl/ *adj., noun*
adj. 1 [only before noun] (often used after *each*) considered separately rather than as part of a group: We interviewed each individual member of the community. ◊ The minister refused to comment on individual cases. 2 [only before noun] connected with one person; designed for one person: respect for individual freedom ◊ an individual pizza 3 (usually approving) typical of one particular person or thing in a way that is different from others **SYN** **distinctive**: a highly individual style of dress

noun 1 a person considered separately rather than as part of a group: The competition is open to both teams and individuals. ◊ Treatment depends on the individual involved. ◊ donations from private individuals (= ordinary people rather than companies, etc.) 2 a person who is original and very different from others: She's grown into quite an individual. 3 (informal, usually disapproving) a person of a particular type, especially a strange one: an odd-looking individual ◊ So this individual came up and demanded money.

in-di-vid-u-al-ism **AWL** /ɪnˈdɪvɪdʒuəlɪzəm/ *noun* [U] 1 the quality of being different from other people and doing things in your own way 2 the belief that individual people in society should have the right to make their own decisions, etc., rather than be controlled by the government: Capitalism stresses innovation, competition and individualism. ► **in-di-vid-u-al-ist** **AWL** /-əlɪst/ *noun*: She's a complete individualist in her art. **in-di-vid-u-al-ist-ic** **AWL** /ɪnˈdɪvɪdʒuəlɪstɪk/ (also **in-di-vid-u-al-ist**) *adj.*: an individualistic culture ◊ His music is highly individualistic and may not appeal to everyone.

in-di-vid-u-al-ity **AWL** /ɪnˈdɪvɪdʒuəlɪti/ *noun* [U] the qualities that make sb/sth different from other people or things: She expresses her individuality through her clothes.

in-di-vid-u-al-ize (BrE also **-ise**) /ɪnˈdɪvɪdʒuəlaɪz/ *verb* ~ sth to make sth different to suit the needs of a particular person, place, etc: to individualize children's learning ► **in-di-vid-u-al-iza-tion**, **-isa-tion** /ɪnˈdɪvɪdʒuəlaɪzɪʃn/; *NAmE* /-əɪz-/ *noun* [U]

in-di-vid-u-al-ized (BrE also **-ised**) /ɪnˈdɪvɪdʒuəlaɪzd/ *adj.* designed for a particular person or thing; connected with a particular person or thing: individualized teaching ◊ a highly individualized approach to management

in-di-vid-u-al-ly **AWL** /ɪnˈdɪvɪdʒuəlɪ/ *adv.* separately, rather than as a group: individually wrapped chocolates ◊ The manager spoke to them all individually. ◊ The hotel has 100 individually designed bedrooms.

in-di-vid-u-ate /ɪnˈdɪvɪdʒuət/ *verb* ~sb/sth (formal) to make sb/sth clearly different from other people or things of the same type

in-di-vis-ible /ɪnˈdɪvɪzəbəl/ *adj.* that cannot be divided into separate parts **OPP** **divisible** ► **in-di-vis-ibil-ity** /ɪnˈdɪvɪzəˈbɪləti/ *noun* [U] **in-di-vis-ibly** /ɪnˈdɪvɪzəbəlɪ/ *adv.*

Indo- /ɪndəʊ/ *NAmE* 'indou/ combining form (in nouns and adjectives) Indian: the Indo-Pakistan border

Indo-Ca-nadian *noun* [C] (CanE) a Canadian who was born in S Asia, especially India, or whose family originally came from S Asia

in-doc-tri-nate /ɪnˈdɒktrɪneɪt/; *NAmE* /nˈdɒk-/ *verb* ~sb (with sth) 1 ~sb (to do sth) (disapproving) to force sb to accept a particular belief or set of beliefs and not allow them to consider any others: They had been indoctrinated from an early age with their parents' beliefs. ► **in-doc-tri-na-tion** /ɪnˈdɒktrɪneɪʃn/; *NAmE* /-dɒk-/ *noun* [U]: political/religious indoctrination

Indo-Euro-pean *adj.* of or connected with the family of languages spoken in most of Europe and parts of western Asia (including English, French, Latin, Greek, Swedish, Russian and Hindi)

in-do-lent /ɪnˈdɒlənt/ *adj.* (formal) not wanting to work **SYN** **lazy** ► **in-do-lence** /-əns/ *noun* [U]

in-dom-it-able /ɪnˈdɒmɪtəbəl/; *NAmE* /nˈdɒm-/ *adj.* (formal, approving) not willing to accept defeat, even in a difficult situation; very brave and determined

in-door **AWL** /ɪnˈdɔː(r)/ *adj.* [only before noun] located, done or used inside a building: an indoor swimming pool ◊ indoor games ◊ the world indoor 200 metres champion **OPP** **outdoor**

in-doors **AWL** /ɪnˈdɔːz/; *NAmE* /nˈdɔːrz/ *adv.* inside or into a building: to go/stay indoors ◊ Many herbs can be grown indoors. **OPP** **outdoors**

in-drawn /ɪnˈdrɔːn/ *adj.* (literary) **indrawn** breath is air that sb breathes in suddenly and quickly, expressing surprise or shock

in-dub-it-ably /ɪnˈdjuːtəbəlɪ/; *NAmE* /-duː-/ *adv.* (formal) in a way that cannot be doubted; without question **SYN** **undoubtedly**: He was, undoubtedly, the most suitable candidate. ► **in-dub-it-able** *adj.*: indubitable proof

in-duce **AWL** /ɪnˈdjuːs/; *NAmE* /-dus-/ *verb* 1 ~sb to do sth (formal) to persuade or influence sb to do sth: Nothing would induce me to take the job. 2 ~sth (formal) to cause sth: drugs which induce sleep ◊ a drug-induced coma 3 ~sb/sth (medical) to make a woman start giving birth to her baby by giving her special drugs ◊ **WORDFINDER** NOTE AT BIRTH: an induced labour ◊ We'll have to induce her.

in-duce-ment /ɪnˈdjuːsmənt/; *NAmE* /-dus-/ *noun* [C, U] ~ (to/for sb) (to do sth) something that is given to sb to persuade them to do sth **SYN** **incentive**: financial inducements to mothers to stay at home ◊ There is little inducement for them to work harder. ◊ Government officials have been accused of accepting inducements (= BRIBES) from local businessmen.

in-duct /ɪnˈdʌkt/ *verb* [often passive] ~sb (into sth) (as sth) (formal) 1 to formally give sb a job or position of authority, especially as part of a ceremony 2 to officially introduce sb into a group or an organization, especially the army 3 to introduce sb to a particular area of knowledge: They were inducted into the skills of magic.

in-duct-ee /ɪnˈdʌkˈtiː/ *noun* (especially *NAmE*) a person who is being, or who has just been, introduced into a special group of people, especially sb who has just joined the army

in-duc-tion **AWL** /ɪnˈdʌkʃn/ *noun* 1 [U, C] ~ (into sth) the process of introducing sb to a new job, skill, organization, etc.; a ceremony at which this takes place 2 [U, C] the act of making a pregnant woman start to give birth, using artificial means such as a special drug 3 [U] (specialist) a method of discovering general rules and principles from particular facts and examples ◊ **COMPARE** **DEDUCTION**

... Problems of family relationships feature prominently in her novels.

prom-is-cu-ous /prə'miskjuəs/ *adj.* (disapproving) **1** having many sexual partners: promiscuous behaviour **2** a promiscuous lifestyle **3** to be sexually promiscuous **2** (formal) taken from a wide range of sources, especially without careful thought: promiscuous reading **3** a stylistically promiscuous piece of music ► **prom-is-cu-ity** /prə'miskju:əti/ *NAmE* **prom-as-i-** *noun* [U]: sexual promiscuity **prom-is-cu-** *adv.*

prom·ise ⓘ /'prɒmɪs; NAmE 'pra:m-/ verb, noun

verb 1 [I, T] to tell sb that you will definitely do or not do sth, or that sth will definitely happen: ~ (to do sth) The college principal promised to look into the matter. ◊ 'Promise not to tell anyone!' I promise. ◊ They arrived at 7.30 as they had promised. ◊ ~ sth The government has promised a full investigation into the disaster. ◊ I'll see what I can do but I can't promise anything. ◊ ~ (that)... The brochure promised (that) the local food would be superb. ◊ ~ sb (that)... You promised me (that) you'd be home early tonight. ◊ ~ sth to sb He promised the money to his grandchildren. ◊ ~ sb sth He promised his grandchildren the money. ◊ ~ yourself sth I've promised myself some fun when the exams are over. ◊ ~ (sb) + speech 'I'll be back soon,' she promised. ➔ MORE LIKE THIS 33, page R16 2 [T] to make sth seem likely to happen; to show signs of sth: it promises to be sth It promises to be an exciting few days. ◊ ~ sth There were dark clouds overhead promising rain. ➔ MORE LIKE THIS 26, page R16

IDM I (can) **'promise you** (*informal*) used as a way of encouraging or warning sb about sth: *I can promise you, you'll have a wonderful time.* ◊ *If you don't take my advice, you'll regret it, I promise you.* **promise (sb) the 'earth/'moon/'world** (*informal*) to make promises that will be impossible to keep

noun 1 [C] a statement that tells sb that you will definitely do or not do sth: to **make/keep/break a promise** ◇ ~ (to do sth) She kept her promise to visit her aunt regularly. ◇ (of sth) The government failed to keep its promise of lower taxes. ◇ ~ (that ...) Do I have your promise that you won't tell anyone about this? ◇ You haven't gone back on your promise, have you? **IDM** SEE LICK n. 2 [U] a sign that sb/sth will be successful **SYN** potential: Her work shows great promise. ◇ He failed to fulfil his early promise. ◇ Their future was full of promise. 3 [U, sing.] ~ of sth a sign, or a reason for hope that sth may happen, especially sth good: The day dawned bright and clear, with the promise of warm, sunny weather.

the Promised Land *noun* [sing.] a place or situation where you expect to be happy, safe, etc.

prom-is-ing /ˈprɒmɪsɪŋ; NAmE ˈprɑːm-/ *adj.* showing signs of being good or successful: He was voted the most promising new actor for his part in the movie. ♦ The weather doesn't look very promising. ► **promisingly** *adv.*: The day began promisingly with bright sunshine.

promissory note /'prɒmɪsəri nəʊt; NAmE 'prɑ:m-
nəʊt/ *noun* (specialist) a signed document containing a
promise to pay a stated amount of money before a par-
ticular date

promo /'prəʊməʊ; NAmE 'prəʊmoʊ/ *adj.* [only before noun] (informal) connected with advertising (= PROMOTING) sb/sth, especially a new pop record: a promo video ▶ **promo** *noun* (pl. -os): to make pop promos

prom-on-tory /'prɒməntəri; NAmE 'prɑ:məntəri/ *noun* (pl. -ies) a long narrow area of high land that goes out into the sea **SYN** headland **➔** WORDFINDER NOTE AT COAST **➔** VISUAL VOCAB PAGE V5

pro·mote ⓘ **AWL** /prə'maʊt: *NAmE* -'mout/ verb


1 **to ~ sth** to help sth to happen or develop **(SYN)** encourage: policies to promote economic growth **to ~ a campaign** to promote awareness of environmental issues 2 **to ~** to help sell a product, service, etc. or make it more popular by advertising it or offering it at a special price: ~ sth The band has gone on tour to promote their new album. **to ~ sth as sth** The area is being promoted as a tourist destination. 3 **[often passive]** to move sb to a higher rank or more senior job: ~

sb She worked hard and was soon promoted. ○ **-sb (from sth) (to sth)** He has been promoted to sergeant. **OPP demote** 4 **~sth (from sth) (to sth)** to move a sports team from playing with one group of teams to playing in a better group: They were promoted to the First Division last season. **OPP relegate**

pro-moter **AWL** /prə'məʊtə(r); NAmE -'mou-/ **noun** **1** a person or company that organizes or provides money for an artistic performance or a sporting event **2** ~**of** sth a person who tries to persuade others about the value or importance of sth **SYN** **champion**: *She became a leading promoter of European integration.*

promotion ⓘ **AWL** /prə'məʊʃn; NAmE -'moʊʃn/
noun 1 ⓘ [U, C] ~ (to sth) a move to a more important job or rank in a company or an organization: *Her promotion to Sales Manager took everyone by surprise.* ◊ *The new job is a promotion for him.* ◊ a job with excellent promotion prospects ⇨ COLLOCATIONS at JOB 2 ⓘ ~ (to sth) a move by a sports team from playing in one group of teams to playing in a better group: *the team's promotion to the First Division*
OPP relegation 3 ⓘ [U, C] activities done in order to increase the sales of a product or service; a set of advertisements for a particular product or service: *Her job is mainly concerned with sales and promotion.* ◊ *We are doing a special promotion of Chilean wines.* ⇨ SEE ALSO CROSS-PROMOTION ⇨ SYNONYMS at ADVERTISEMENT ⇨ WORDFINDER
NOTE at SHOP 4 ⓘ ~ of sth (formal) activity that encourages people to believe in the value or importance of sth, or that helps sth to succeed: *a society for the promotion of religious tolerance*

pro-mo-tion-al /prə'məʊʃənəl; NAmE -'mou-/ *adj.* connected with advertising: *promotional material*

prompt  /prɒmpt; NAmE pra:mpt/ *adj.*, *verb*, *noun*, *adv*

adj. 1 **✓** done without delay **SYN** immediate: Prompt action was required as the fire spread. ◊ Prompt payment of the invoice would be appreciated. 2 **✓** [not before noun] (of a person) acting without delay; arriving at the right time **SYN** punctual: Please be prompt when attending these meetings. ► **prompt-ness** noun [U]

verb 1 **[T]** to make sb decide to do sth; to cause sth to happen **SYN** **provoke**: ~sth The discovery of the bomb prompted an increase in security. ◊ His speech prompted an angry outburst from a man in the crowd. ◊ ~sb to do sth The thought of her daughter's wedding day prompted her to lose some weight. 2 **[T]** to encourage sb to speak by asking them questions or suggesting words that they could say: ~sb She was too nervous to speak and had to be prompted. ~sb to do sth (computing): The program will be prompted to enter data where required. ◊ ~ (sb) + speech 'And then what happened?' he prompted. 3 **[T, I]** ~ (sb) to follow the text of a play and remind the actors what the words are if they forget their lines

- **noun** 1 a word or words said to an actor, to remind them what to say next when they have forgotten 2 (computing) a sign on a computer screen that shows that the computer has finished doing sth and is ready for more instructions
- **adv.** exactly at the time mentioned: *The meeting will begin at ten o'clock prompt.*

prompt-er /'promptə(r); NAmE 'pra:m-/ *noun* a person who prompts actors in a play ➔ **WORDFINDER NOTE AT PERFORMANCE**

prompting /'promptɪŋ; NAmE 'pra:m-/ noun [U] (also **promptings** [pl.]) an act of persuading sb to do sth: He wrote the letter without further **prompting**. ♦ Never again would she listen to the **promptings** of her heart.

promptly ⓘ /ˈprɒmptli: NAmE 'pra:m-/ *adv*

promptly /prɒmptli, /pʁɑ̃pt/ *promptly* 1 **1** without delay: *She deals with all the correspondence promptly and efficiently.* 2 **2** exactly at the correct time or at the time mentioned **SYN** *punctually*: *They arrived promptly at two o'clock.* 3 (always used before the verb) immediately: *She read the letter and promptly burst into tears.*

EXHIBIT 10

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in-di-vid-u-al-ism /ɪndəˈvɪdʒuəlɪzəm/ (AWL) *n.* [U] 1 the behavior or attitude of someone who does things in his/her own way without being influenced by other people: *The culture of the western U.S. has always valued rugged individualism.* 2 the belief that the rights and freedom of individual people are the most important rights in society: *Japanese society promotes the group rather than individualism.* —**individualist** *n.* [C]: *He was an individualist who always spoke his mind.* —**individualistic** /ɪndəˈvɪdʒuəlɪstɪk/ *adj.*

in-di-vid-u-al-i-ty /ɪndəˈvɪdʒuələti/ ●●● *n.* [U] the quality that makes someone or something different from all others: *His individuality shows in his art work.*

in-di-vid-u-al-ly /ɪndəˈvɪdʒuəli, -dʒəli/ ●●● (AWL) *adv.* separately, not together in a group: *Mr. Wong met with each employee individually.*

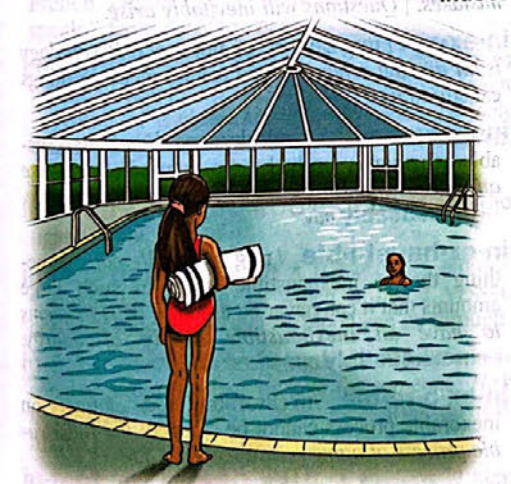
in-di-vis-i-ble /ɪndəˈvɪzəbəl/ *adj.* not able to be separated or divided into parts —**indivisibly** *adv.*

in-doc-tri-nate /ɪnˈdɑktreɪn/ *v.* [T] disapproving to teach someone to accept a particular set of beliefs and not consider any others —**indoctrination** /ɪnˈdɑktreɪnəʃən/ *n.* [U]

in-do-lent /ɪndələnt/ *adj.* formal lazy —**indolently** *adv.* —**indolence** *n.* [U]

in-dom-i-ta-ble /ɪnˈdɑmətəbəl/ *adj.* indomitable **spirit/courage etc.** formal determination, courage, etc. that can never be defeated

indoor



indoor swimming pool

in-door /ɪndɔːr/ ●●● *adj.* [only before noun] used for happening inside a building (ANT) **outdoor**: *an indoor swimming pool*

in-doors /ɪnˈdɔːr/ ●●● *adv.* into or inside a building (ANT) **outdoors**: *He stayed indoors all morning.*

in-duce /ɪnˈdus/ ●●● (AWL) *v.* formal 1 [T] to make someone decide to do something: *What induced you to spend so much money on a car?*

industrial park

THESAURUS

cause, make, prompt

→ CAUSE²

2 [T] to cause a particular physical condition: *This drug may induce drowsiness.* 3 [I,T] **MEDICINE** to make a woman give birth to her baby by giving her a special drug

in-duce-ment /ɪnˈdusmənt/ *n.* [C,U] something that you are offered to persuade you to do something: *He was given \$10,000 as an inducement to leave the company.*

in-duct /ɪnˈdʌkt/ *v.* [T] to officially make someone a member of a group or organization: *Joni Mitchell was inducted into the Rock and Roll Hall of Fame.* —**inductee** /ɪnˈdʌkˈti/ *n.* [C]

in-duc-tion /ɪnˈdʌkʃən/ *n.* [C,U] the act or ceremony of officially making someone a member of a group or organization

in-duc-tive /ɪnˈdʌktɪv/ *adj.* using known facts or patterns to form the general principles of something or a general opinion about something: *inductive research*

in-ductive 'reasoning *n.* [U] **MATH** the process of forming a general mathematical rule for solving a mathematical problem using an existing pattern of specific results or facts

in-dulge /ɪnˈdʌldʒ/ ●●● *v.* 1 [I,T] to let yourself do or have something that you enjoy, especially something that is considered bad for you: *We indulged in a piece of cheesecake after lunch.* | *Go ahead – indulge yourself.* 2 [T] to let someone do or have whatever s/he wants, even if it is bad for him/her: *She did not like her children to be indulged.*

in-dul-gence /ɪnˈdʌldʒəns/ *n.* 1 [U] the habit of eating too much, drinking too much, etc.: *a life of indulgence* 2 [C] something that you do or have for pleasure, not because you need it: *Chocolate is my only indulgence.*

in-dul-gent /ɪnˈdʌldʒənt/ *adj.* allowing someone to do or have whatever s/he wants, even if it is bad for him/her: *indulgent parents* —**indulgently** *adv.*

in-dus-tri-al /ɪnˈdʌstriəl/ ●●● *adj.* 1 relating to industry or the people working in industry: *industrial waste* | *industrial production* 2 having many industries, or industries that are well developed: *an industrial region* —**industrially** *adv.*

in-dus-tri-al-ist /ɪnˈdʌstriəlɪst/ ●●● *n.* [C] the owner of a factory, industrial company, etc.

in-dus-tri-al-ize /ɪnˈdʌstriələɪz/ *v.* [I,T] if a country or place is industrialized, or if it industrializes, it develops a lot of industry —**industrialization** /ɪnˈdʌstriələɪzəʃən/ *n.* [U]

in-dus-tri-al-ized /ɪnˈdʌstriələɪzd/ ●●● *adj.* **SOCIAL STUDIES** having factories, mines, industrial companies, etc. on a very wide scale: *industrialized nations*

in-dus-tri-al park *n.* [C] an area of land that has offices, businesses, small factories, etc. on it

pro-mis-cu-ous /prə'miskyuəs/ *adj.* formal having sex with a lot of people — **promiscuity** /prə'miskyuəti/ *n.* [U]

prom-ise¹ /'pramis/ ●●● *v.* 1 [I,T] to tell someone that you will definitely do something, or that something will definitely happen: *Police have promised a full investigation.* | *I promised Barbara (that) I'd meet her after work.* | *I promise (that) I'll never do that again.* | *Both candidates promised to get tougher on crime.* | *I've already promised them a ride to the dance.*

THESAURUS

give sb your word — to promise someone very sincerely that you will do something: *He gave us his word and I believe him.*

swear — to make a very serious promise: *He had sworn not to reveal her secret.*

take/swear an oath — to make a very serious promise in public: *You must take an oath of loyalty to your country.*

vow — to make a serious promise, often to yourself: *She vowed that she would never drink alcohol again.*

pledge — to make a formal, usually public, promise: *Canada pledged to provide medical aid.*

undertake to do sth *formal* — to promise or agree to do something: *I undertook to support her, clothe her, and protect her.*

guarantee — to promise something that you feel very sure about: *I can guarantee you a ten percent increase on your current salary.*

commit — to say that you will definitely do something: *The company had committed to finishing the project by June 20.*

2 [T] to make people expect that something will happen: *The game promises to be exciting.*

3 **I can't promise anything** *spoken* used in order to tell someone that you will try to do what s/he wants, but you may not be able to do it [Origin: 1300–1400 Latin *promissum*, from the past participle of *promittere* “to send out, promise”]

promise² ●●● *n.* 1 [C] a statement that you will definitely do something, or that something will definitely happen: *She made a promise to take care of her neighbor's dog.* | *I didn't want to break my promise (=not do what I said I would do).* | *Has the president kept his promise to increase funding for education?* | *She got promises of help from friends and family.* 2 [U] signs that something or someone will be good or successful: *He shows a lot of promise as a writer.*

COLLOCATIONS

VERBS

to make a promise *She made a promise to write to him every day.*

to keep a promise also to fulfill a promise *formal* (=to do what you promised to do) *I kept my promise and gave her half the money.*

to break a promise (=to not do what you promised to do) *After he was elected, he broke a lot of his campaign promises.*

ADJECTIVES/NOUNS + promise

a false/empty promise (=one that will not be kept) *I'm tired of his empty promises — he never does what he says he'll do.*

a broken promise (=one that has not been kept) *I don't trust her. It's just broken promise after broken promise with her.*

a solemn promise *The judge asked the jury for their solemn promise not to watch television news during the trial.*

a campaign/election promise *She kept her campaign promise to get the law passed.*

prom-is-ing /'pramisɪŋ/ ●●● *adj.* showing that someone or something is likely to be successful in the future: *a promising young singer* — **promisingly** *adv.*

pro-mo /'proumou/ *n.* (plural **promos**) [C] *informal* a PROMOTION

prom-on-to-ry /'pramən'tɔ:ri/ *n.* (plural **promontories**) [C] **GEOGRAPHY, EARTH SCIENCE** a high piece of land that goes out into the ocean

pro-mote /prə'mout/ ●●● (AWL) *v.* [T] 1 to help something develop and be successful: *The bureau's job is to promote tourism to the area.* | *A balanced diet promotes good health.* 2 to give someone a better, more responsible position at work (ANT) **demote**: *Ted was promoted to senior sales manager.* 3 to advertise a product or event: *The author went on a national tour to promote the book.*

THESAURUS

advertise, market, publicize, hype, plug → ADVERTISE

4 to be responsible for arranging a large public event such as a concert or a sports game [Origin: 1300–1400 Latin, past participle of *promovere* “to move forward”]

pro-mot-er /prə'moutə/ *n.* [C] someone whose job is to arrange large public events such as concerts or sports games

pro-mo-tion /prə'mouʃən/ ●●● *n.* [C,U] 1 a move to a better, more responsible position at work: *She received a promotion to lieutenant.* 2 an activity intended to advertise a product or event, or the thing that is being advertised: *a sales promotion*

pro-mo-tion-al /prə'mouʃənəl/ *adj.* promotional products and activities are made or organized in order to advertise something

prompt¹ /præmpt/ ●●● *v.* 1 [T] to make someone do something, or to help him/her remember to do it: *The changes prompted several people to resign from the committee in protest.*

THESAURUS

cause, make, result in sth, lead to sth, trigger, induce → CAUSE²

2 [I,T] **ENG. LANG. ARTS** to remind someone, especially an actor, of the next words in a speech [Origin: 1300–1400 Medieval Latin *promptare*, from Latin *promptus*, from the past participle of *promere* “to bring out”]

EXHIBIT 11

LATHAM & WATKINS LLP

330 North Wabash Avenue
Suite 2800
Chicago, Illinois 60611
Tel: +1.312.876.7700 Fax: +1.312.993.9767
www.lw.com

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June 30, 2023


VIA E-MAIL

Gabriel Brier
Quinn, Emmanuel, Urquhart, and Sullivan, LLP
51 Madison Avenue, 22nd Floor
New York, NY 10010

Re: Improper Arguments in Jazz’s Expert Rebuttal Reports

Dear Gabe:

We write in response to your June 6, 2023 letter regarding the undisclosed claim construction positions taken by Jazz’s experts. In that letter, Jazz purported not to understand what prejudice could flow from Jazz switching positions and otherwise obfuscating its arguments as to what several asserted claims require – for example, Jazz relies on the fact that “neither Jazz nor its experts have affirmatively taken the position that the preambles are not claim limitations.” Ltr. at 3. Jazz is well aware that it is prejudicial that Avadel does not know how Jazz plans to interpret the scope of the claims at trial. Jazz’s decision to double down and assert that it is free to keep its options open on such basic questions as whether claim limitations are non-limiting confirms the prejudice. If Jazz persists in pursuing the new theories that we previously identified, Avadel will seek to have those new opinions excluded from trial. We respond briefly to Jazz’s points

I. JAZZ CANNOT CONTEND THE PREAMBLES ARE NOT LIMITING

In our initial letter, we itemized Jazz’s assertions, in its infringement contentions, that the preambles in question were claim limitations. Nothing in Jazz’s responsive letter addresses this issue. Jazz instead inexplicably contends that it has not taken the position that the preambles are not limiting. But that is exactly what Jazz’s experts did. Dr. Moreton did so in the portion Jazz points to in support of Jazz’s theory that it has not taken a position – Jazz quotes paragraph 109 of Dr. Moreton’s report, in which Dr. Moreton explains just the opposite, stating “Avadel did not take the position during claim construction that the preambles are claim limitations ***In my opinion they are not.***” *Id.* (quoting Moreton Rebuttal Rpt. at ¶ 109) (emphasis added); *see also* Little Rebuttal Rpt. at ¶ 50, 74 (opining that it is not required that the claimed invention “be able to safely or effectively treat narcolepsy”); *id.* at ¶ 74 (classifying the requirement that the claimed oxybate formulation be administered in a single-daily dose to a patient for the treatment of narcolepsy as a “non-existent claim element”); Davies Rebuttal Rpt. at ¶ 44 (opining that that “the claimed methods are performed as long as the steps set forth in the ***claim body*** (i.e. opening, mixing, orally administering) are performed”).

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Given that Jazz now contends it never took the position that the preambles are not limiting, we understand Jazz to be conceding that they are, and that no Jazz expert will assert otherwise. Certainly, any effort by Jazz or its experts to take a different position in the future will be late and prejudicial. Such a switch would also be contrary to Federal Circuit precedent: Jazz does not and cannot dispute that its claims have no proper antecedent basis without reference to the preamble. '079 Patent at Claims, 1, 10 (referencing “administering a single daily dose to *the patient*”) (emphasis added); *id.* at Claims 5 and 14 (referencing a method “wherein the administering promotes *the patient* to sleep for 6 to 8 hours”) (emphasis added); *id.* at Claims 6 and 14 (referencing a method “wherein the amount of oxybate administered to *the patient*” is of disclosed amounts) (emphasis added); '931 Patent at Claim 1 (referencing “delivering to *the patient* a formulation”) (emphasis added); '956 Patent at Claim 1 (referencing “delivering to *the patient* a formulation”). *See, e.g. Haemonetics Corp. v. Baxter Corp.*, 607 F.3d 776, 781-82 (Fed. Cir. 2010) (finding the preamble limiting because the preamble defined “the centrifugal unit” and the claim body further recited “not *a* centrifugal unit, but *‘the* centrifugal unit”) (emphasis in original); *Eli Lilly and Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1343 (Fed. Cir. 2021) (finding the preamble limiting in part because the term “administering to *the individual*” had an antecedent basis in “the preamble term ‘treating ... in *an individual*”). *Jansen* does not require that “the body of the claim” contain the phrase “in need” in order to construe a preamble as limiting. Indeed, the Federal Circuit preempted this very argument in the same opinion. *See id.* (“We need not decide whether we would reach the same conclusion if either the “treating or preventing” phrase or the “to a human in need thereof” phrase *was not part of the claim*; together, however, they compel the claim construction” that the preamble is limiting).

II. JAZZ DID NOT ASK FOR THE CONSTRUCTION “ATTEMPT TO CAUSE A THERAPEUTIC IMPROVEMENT,” WHICH IN ANY EVENT IS NOT THE CONSTRUCTION JAZZ’S EXPERTS ARE USING

Jazz’s new contention that the claim limitations in question require something like an “attempt to cause a therapeutic improvement” is just that – new, and not timely raised before, as we itemized previously. *Ltr.* at 2. It is also wrong. Judge Williams recently rejected just such an argument. *See Novartis Pharms. Corp. v. Hec Pharm Co., Ltd.*, No. 20-1330-GBW, at *6-7 (D. Del. Apr. 6, 2023) (“*Novartis II*”). In *Novartis II*, the defendant argued that a preamble reciting “a method for treating relapsing-remitting multiple sclerosis in a patient in need thereof,” was a “[l]imiting statement of purpose that d[id] not require efficacy.” *Id.* at *7. Judge Williams disagreed, explaining that “excluding efficacy, . . . would import a negative limitation into the preamble untethered from the intrinsic record, and would undermine the general purpose of the invention of the ’179 patent: to achieve a safe and effective manner of treating multiple sclerosis, or an efficacious purpose.” *Id.* at *6-7; *see also id.* at *6. Other courts have construed “method of treating” language in a preamble to require a result of alleviating symptoms of the disease at issue. *In re 318 Patent Infringement Litig.*, 578 F. Supp. 2d 711, 725 (D. Del. 2008) (construing a “method of treating” to mean “[a] method of alleviating the symptoms or deferring the decline associated with [the relevant disease].”). Jazz is not free to act as though it raised this issue, briefed, it, and won. It did none of those things.

While Jazz cites *Novartis Pharms. Corp. v. Actavis, Inc.* (“*Novartis I*”) for the proposition that “the term ‘treating’ does not include a safety or efficacy requirement,” that stretches the

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holding of that case beyond what is justified. No. 12-366, 2013 WL 6142747, at *11 (D. Del. Nov. 21, 2013). *Novartis I* does not stand for the proposition that “treating” does not require safety or efficacy, merely that it does not require “certainty that success will be achieved.” *Id.* *Novartis I* is clear that “treating” “must connote something other than the physical act of ‘administering the claimed compounds.’” *Id.* As Jazz acknowledges, *Novartis I* still requires that a therapy be administered in an “attempt to cause a therapeutic improvement.” *Jun. 6, 2023 Ltr. from G. Brier to A. Sawyer at 4* (citing *id.*). Yet Jazz’s experts contend that the claims require nothing more than “opening, mixing, [and] orally administering,” inappropriately rendering the preamble language as surplusage. Davies Rebuttal Rpt. at ¶ 44; *see also* Little Rpt. ¶ 51 (explaining that the “single daily dose” claim language of the 079 patent does not change his opinion that the claims do not have safety or efficacy requirements, and instead only require that “one dose per day be administered”). Thus, even under Jazz’s claim construction theory as expressed in its June 6 letter, Jazz’s experts took a different view.

The other cases cited by Jazz are similarly inapposite. Many are from unrelated district courts, and the Federal Circuit cases Jazz cites are distinguishable. Jazz cites *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.* for the proposition that the “preamble did not require safety or efficacy where the steps of the claimed ‘method are performed in the same way regardless whether or not the patient experiences a [certain measure of efficacy].” *Id.* (quoting 246 F.3d 1368, 1375 (Fed. Cir. 2001)). Yet that claim term, “for reducing hematologic toxicity,” did not include the word “treating,” and was part of a preamble that was found to be entirely non-limiting. *Id.* Thus, it is inapplicable to the current dispute. Jazz’s reliance on *Sanofi Mature IP v. Mylan Laboratories Ltd.* is similarly misplaced. 757 F. App’x 988, 992-93 (Fed. Cir. 2019). Jazz relies on *Sanofi Mature IP* to argue that a preamble is only limiting “where a method claim preamble sets forth an objective and the body of the claim directs that the method be performed on a patient “in need.” *Jun. 6, 2023 Ltr. from G. Brier to A. Sawyer at 4-5 n.3.* But *Sanofi Mature IP* is not so narrow a holding. The key issue in *Sanofi Mature IP* was not the presence of the language “in need thereof,” but rather that there was “a direct link between the claim as a whole and the preamble, **which provides an antecedent basis** for ‘in need thereof.’” *Sanofi Mature IP*, 757 Fed. App’x at 993 (emphasis added). Indeed, *Sanofi Mature IP* distinguishes *Bristol-Myers Squibb*’s holding on this very basis. *Id.* (explaining that Mylan’s “reliance on *Bristol-Myers Squibb* [was] misplaced” because the preambles there did not “provide[] an antecedent basis” linking the preamble to the claim body’s language). As discussed above, the preambles of Jazz’s claims are necessary to provide antecedent basis for its claims, and are therefore governed by *Sanofi Mature IP*, not *Bristol-Myers Squibb*.

In addition to these flaws in Jazz’s arguments regarding an efficacy requirement, Jazz inappropriately attempts to use its efficacy arguments to bootstrap its assertion that its methods of treating patients need not do so safely. *Celgene* is the only case cited by Jazz where “treating” as used in the preamble was found not to require safety. *Celgene*, 2020 WL 3249117, at *6. However, the *Celgene* court reached that conclusion after finding that the preamble was **not limiting**. *Id.* at *4. A non-limiting term of course requires nothing. In contrast, Jazz here, admits that the preamble is in fact, limiting. *Celgene* is therefore inapposite and no other case that Jazz cites held that safety is not required by the term “treating.”

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III. JAZZ CANNOT READ OUT THE “SINGLE DAILY DOSE” LIMITATION

As Avadel has consistently argued, the “single daily dose” limitation in the ’079 patent requires safety and efficacy, as explained in *Allergan Sales*.

While Jazz contends that Avadel “offered a proposed construction of “single daily dose” in its contentions . . . and did not take the position that the term imparted a safety or efficacy limitation,” that is not true. Avadel took the position that the “single daily dose” limitation of the ’079 patent requires that the single daily dose “*replace* a patient’s *need* to take multiple doses a day.” Avadel’s Final Validity Contentions, at 243, n.39. This requires that the single daily dose provide therapeutic efficacy in a manner that obviates the need to take multiple doses. Avadel also raised therapeutic efficacy in its Interrogatory Responses. See Avadel’s Suppl. Response to Interrogatory 8 at 38 (highlighting “[t]he lack of any *in vitro* or *in vivo* data, or even methods of evaluating the claimed invention for its ability to *function therapeutically as a single daily dose*”).

As to *Allergan Sales*, Jazz’s response misapprehends the holding. Jazz’s contention that the claims were “construed to require safety and efficacy because the prosecution history ‘demonstrate[d] that the formulation’s efficacy and safety,’” does not reflect the case’s full holding. The Federal Circuit held that the “specification of the Patents-in-Suit demonstrate[d] that the claimed invention is ultimately a formulation (and methods of using that formulation) that allows for increased efficacy and safety.” *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1375 (Fed. Cir. 2019). The same is true here. Jazz does not dispute that the specification of the ’079 patent demonstrates that Jazz believed the “efficacy and safety of the claimed methods to be material to patentability,” *Allergan Sales, LLC*, 935 F.3d at 1375. And indeed could not do so, for the reasons explained in our May 30th Letter. *May 30, 2023 Ltr. from A. Sawyer to G. Brier at 5-6*. Contrary to Jazz’s assertions, the prosecution history in *Allergan* was “consistent with th[e] understanding” of the purpose of the invention drawn from the specification, but was not the basis for it. *Id.*

Regardless, even consistent with Jazz’s understanding of *Allergan Sales*, Jazz’s prosecution history shows that Jazz relied upon the therapeutic efficacy of its single daily dose to respond to the Examiner’s rejections. ’079 Patent File History, May 20, 2021 Remarks at 8 (Jazz distinguishing its pending claims from the prior art because the prior art did not teach or suggest the “once daily administration to treat an oxybate-treatable condition”); *id.* at 11 (Jazz distinguishing its pending claims from the prior art because “when the present application was filed, it was understood in the art that oxybate required twice-daily administration to be therapeutically effective”); *id.* at 12 (Jazz distinguishing its pending claims from the prior art because “[i]n contrast [to the prior art], the presently-claimed methods provide therapeutic effectiveness through once daily administration”). Here, it is clear that Jazz understood its invention to “provide therapeutic effectiveness through once daily administration.”

IV. JAZZ CANNOT READ OUT LIMITATIONS OF CLAIMS 5 AND 14 OF THE ’079 PATENT

Jazz contends that the wherein clauses of claims 5 and 14 of the ’079 patent are merely “an aspiration result” and are not claim limitations. *June 6, 2023 Ltr. from G. Brier to A. Sawyer*

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at 6; Little Rebuttal Rpt. at ¶ 62 (explaining that “it is my opinion that the plain and ordinary meaning of the wherein clause in the ’079 patent, claims 5 and 14, is only an intended result of administration of the formulation described in the claims” and “wherein clauses regarding efficacy are not limiting when they merely express the intended result”). As previously explained, Jazz unambiguously took the opposite position in its Final Contentions and cannot now, through the Rebuttal Report of Dr. Little, introduce a novel construction never previously raised.

5. The method of claim 1,	See claim 1.
wherein the administering promotes the patient to sleep for 6 to 8 hours.	The use of Avadel’s NDA Product will literally meet this limitation. This is supported by Avadel’s document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.
14. The method of claim 10,	See claim 10.
wherein the administering promotes the patient to sleep for 6 to 8 hours.	The use of Avadel’s NDA Product will literally meet this limitation. This is supported by Avadel’s document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.

May 30, 2023 Ltr. from A. Sawyer to G. Brier at 2 (citing Plaintiff’s Final Infringement Contentions at 212, 219).

Further, despite Jazz’s attempts to find a distinction, *L’Oreal USA, Inc. v. Olaplex, Inc.* is squarely on point. As previously explained, where dependent claims contain “specific requirements” and that “is all they do,” treating those “limitations as of no legal effect would be to interpret each of these dependent claims as entirely a nullity.” 844 Fed. App’x 308, 324 (Fed. Cir. 2021). Jazz contends that *L’Oreal* is distinguishable because the claims there “state[d] specific requirements [i.e., specific numerical decreases in “hair breakage”]” and claims 5 and 14 merely state “an aspirational result.” *June 6, 2023 Ltr. from G. Brier to A. Sawyer at 6*. But claims 5 and 14 of the ’079 patent do contain specific requirements. The wherein clauses recite “promot[ing] the patient to sleep for **6 to 8 hours**.” ’079 Patent at claims 5, 14 (emphasis added); *L’Oreal USA, Inc.*, 844 Fed. App’x at 324 (explaining that the “specific decreases (*e.g.*, 5%, 10%, 20%, 40%, 50%) in hair breakage” amounted to “stat[ing] specific requirements rather than a general purpose or aspirational result”). Contrary to Jazz’s arguments, *L’Oreal* is controlling.

Please confirm promptly whether Jazz agrees to withdraw the opinions identified herein. If not, please provide your availability to promptly meet and confer.

Sincerely,

/s/ Alex M. Grabowski
Alex M. Grabowski
of LATHAM & WATKINS LLP

EXHIBIT 12

555 Eleventh Street, N.W., Suite 1000
Washington, D.C. 20004-1304
Tel: +1.202.637.2200 Fax: +1.202.637.2201
www.lw.com

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May 30, 2023

VIA E-MAIL

Gabriel Brier
Quinn, Emmanuel, Urquhart, and Sullivan, LLP
51 Madison Avenue, 22nd Floor
New York, NY 10010

Re: Improper Arguments in Jazz's Expert Rebuttal Reports

Dear Counsel:

We write regarding the rebuttal expert Reports of Drs. Moreton, Little, and Davies, which introduce previously undisclosed claim construction positions.

Specifically, in Paragraph 109 of his Report, Dr. Moreton takes the position that the “method of treating” language in the preambles of claim 1 of both the ’931 and the ’956 patents are not claim limitations, “let alone limitations that add any safety or efficacy requirements to the claims.” In Paragraph 50 of his Report, Dr. Little takes the same position with respect to the ’079 patent that the “method of treating” language in the preambles of claims 1 and 10 are not claim limitations, “let alone limitations that add any safety or efficacy requirements.” Dr. Little also opines that the “single daily dose” language in claims 1 and 10 of the ’079 patent “does not change [his] opinion” that the claims do not contain any “safety or efficacy requirement” and that this language requires only that “one dose per day be administered,” not that it has any intended purpose or required result. Little Rebuttal Rpt. ¶ 51. Likewise, Dr. Little alleges that the “wherein clauses” (*i.e.*, the entirety of what is added by) of dependent claims 5 and 14 are not limiting, and recite “only an intended result” of administering the claimed formulation. Little Rebuttal Rpt. ¶ 62. In short, Dr. Little has opined that he believes the claims do not contain any requirement that the claimed oxybate formulation be administered as a single daily dose that can be used to treat narcolepsy, cataplexy, or excessive daytime sleepiness. *See id.* at ¶¶ 50-55, 62. Dr. Davies presents similar opinions, and asserts that a POSA would understand that the methods of claims 1 and 10 of the ’079 patent “are performed so long as the steps set forth in the claim body (*i.e.*, opening, mixing, orally administering) are performed.” Davies Rebuttal Rpt. ¶¶ 43-44.

Thus, Drs. Moreton, Little, and Davies introduce three new and improper arguments: (1) that the preambles of claims 1 and 10 of the ’079 patent, claim 1 of the ’931 patent, and claim 1 of

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the '956 patent are not limiting and do not impose a safety or efficacy requirement; (2) that the "single daily dose" limitation in claims 1 and 10 of the '079 patent does not impose any safety or efficacy requirement; and (3) that the limitations added by dependent claims 5 and 14 of the '079 patent are non-limiting. These opinions are improper under the Court's procedures and the Scheduling Order and should be withdrawn. And in any event, they are legally frivolous.

I. Jazz's Belated Claim Construction Positions Were Not Properly Disclosed

As an initial matter, none of Jazz's arguments were properly disclosed in Jazz's infringement or validity contentions. To the contrary, before the parties exchanged disputed claim terms, Jazz took the exact opposite position in its Initial Infringement Chart by arguing that Avadel's LUMRYZ product infringes the asserted claims because it will "literally meet" the limitations reciting "treating narcolepsy" and "treating cataplexy" by "treat[ing] narcolepsy" and "treat[ing] cataplexy":

'079 Patent	Avadel's NDA Product
1. A method of treating narcolepsy in a patient in need thereof, the method comprising:	<p>The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.</p> <p>The administration of Avadel's NDA Product will treat narcolepsy in a patient in need thereof. See AVDL_00045593; AVDL_00045600; AVDL_00045606; AVDL_00045610; AVDL_00052477-78; AVDL_00052493; AVDL_00102530-32; AVDL_00102548-49.</p>
10. A method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof, the method comprising:	<p>The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.</p> <p>The administration of Avadel's NDA Product will treat cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof. See AVDL_00045593; AVDL_00045600; AVDL_00045606; AVDL_00045610; AVDL_00052477-78; AVDL_00052493; AVDL_00102530-32; AVDL_00102548-49.</p>

Jazz took similarly unambiguous positions with respect to claims 5 and 14, never disclosing that the "wherein" clauses were "not limiting" as Jazz's experts belatedly assert now:

5. The method of claim 1,	See claim 1.
wherein the administering promotes the patient to sleep for 6 to 8 hours.	The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.
14. The method of claim 10,	See claim 10.
wherein the administering promotes the patient to sleep for 6 to 8 hours.	The use of Avadel's NDA Product will literally meet this limitation. This is supported by Avadel's document production, and may be further supported by additional fact discovery that has not yet occurred, and/or by evidence obtained and/or generated as part of expert discovery.

Jazz's experts half-heartedly blame Avadel for their previously-undisclosed claim construction opinions. See Little Rebuttal Rpt. ¶ 50 ("I understand from counsel that the 'method of treating' language appears in the preambles, or the beginning portions, of the claims and that

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Avadel did not take the position during claim construction that the preambles are claim limitations, let alone ones that add any safety or efficacy requirements.”); Moreton Rebuttal Rpt. ¶ 109 (“I understand from Jazz’s attorneys, however, that Avadel did not take the position during claim construction that the preambles are claim limitations, let alone limitations that add any safety or efficacy requirements to the claims.”).

However, as addressed above, Jazz unambiguously treated the claim elements at issue as limitations, and Avadel reasonably relied on those positions during the claim construction process, according to the Court’s procedures. Jazz cannot now blame Avadel for relying on Jazz’s infringement contentions which, indeed, are intended to identify claim construction disputes early in the case. At no time between service of its Initial Infringement Chart on December 7, 2021 and the exchange of disputed claim terms on February 18, 2022 did Jazz indicate that it intended to argue that these terms were non-limiting. And in fact, Jazz repeatedly confirmed this position until service of its expert reports this month:

- Plaintiff’s Final Infringement Contentions at 207 (alleging without qualification that “Avadel’s NDA Product will literally meet [the preamble’s] limitation” for claim 1 of the ’079 patent because it “will treat narcolepsy in a patient in need thereof”);
- Plaintiff’s Final Infringement Contentions at 214 (alleging without qualification that “Avadel’s NDA Product will literally meet [the preamble’s] limitation” for claim 10 of the ’079 patent because it “will treat cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof”);
- Plaintiff’s Final Infringement Contentions at 208 (alleging that without qualification “Avadel’s NDA Product will literally meet [the single daily dose to the patient] limitation for claim 1 of the ’079 patent because treatment “will be administered in a single daily dose”);
- Plaintiff’s Final Infringement Contentions at 178 (alleging without qualification that “Avadel’s NDA Product will literally meet [the preamble’s] limitation” for claim 1 of the ’931 patent because it “will treat cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof”);
- Plaintiff’s Final Infringement Contentions at 108 (alleging without qualification that “Avadel’s NDA Product will literally meet [the preamble’s] limitation” for claim 1 of the ’956 patent because it will “treat cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof”);
- Plaintiff’s Final Infringement Contentions at 212 (alleging without qualification that “Avadel’s NDA Product will literally meet [the limitation of promoting a “patient to sleep for 6 to 8 hours”] because it will ‘allow [] patients at least six hours of continuous and improved sleep’ and because “plasma GHB concentration [will be] maintained throughout the night, as well as gradual[ly] decline to lowest levels by 8-10 hours after dosing”) (emphasis added);

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- Plaintiff's Final Infringement Contentions at 219 (alleging without qualification that "Avadel's NDA Product will literally meet the limitation of promoting a "patient to sleep for 6 to 8 hours"] because it will 'allow [] patients at least six hours of continuous and improved sleep' and because "plasma GHB concentration [will be] maintained throughout the night, as well as gradual[ly] decline to lowest levels by 8-10 hours after dosing") (emphasis added);
- Jazz's Responses to Defendants' Validity Contentions at 95, 97 (listing, without qualification, alleged written description support for preamble of claims 1, 10);
- Jazz's Responses to Defendants' Validity Contentions at 95, 97 (listing, without qualification, alleged written description support for single dose limitation of claims 1, 10); and
- Jazz's Responses to Defendants' Validity Contentions at 96 and 98 (listing, without qualification, alleged written description support for dependent claims 5 and 14 based on a disclosure that "the concentration of GHB in the blood" should be maintained at sufficient levels).

Jazz's shifting sands approach to claim construction is inappropriate and violates this Court's procedures.

II. Jazz's Claim Construction Arguments are Incorrect

a. Jazz is wrong that the preambles of claims 1 and 10 of the '079 patent, claim 1 of the '931 patent, and claim 1 of the '956 patent are not limiting

In addition to being raised far too late in light of the provisions of the Scheduling Order, Jazz's argument that the preambles of the independent claims in the '079 patent, the '931 patent, and '956 patent are non-limiting is in direct conflict with Federal Circuit precedent for three reasons. First, the Federal Circuit has long found that the preamble "gives life and meaning" to a claim and that "what a method does is usually recited in its preamble." *Eli Lilly and Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1341 (Fed. Cir. 2021); *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003); *see also Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003) (explaining that the preamble of the method claims were "not merely circumstances in which the method may be useful, but instead [were] the *raison d'être* of the claimed method itself"). Consequently, "claim construction analysis of statements of intended purpose in methods of using apparatuses or compositions has tended to result in a conclusion that such preamble language is limiting." *Id.* Indeed, the Federal Circuit has held that preambles reciting that methods to "be performed on someone 'in need'" are limiting. *Jansen*, 342 F.3d at 1333; *Rapoport v. Dement*, 254 F.3d 1053, 1059 (Fed. Cir. 2001).

Second, the Federal Circuit has held that a preamble limits the scope of a claim when "the preamble provides antecedents for ensuing claim terms and limits the claim accordingly." *Boehringer*, 320 F.3d at 1345. Here, the preambles identify the relevant patient groups. Indeed, the term "patient" has no proper antecedent basis without reference to the preamble. *Rapoport*,

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254 F.3d at 1059 (explaining that “without treating the [preamble’s] phrase ‘treatment of sleep apneas’ as a claim limitation, the phrase ‘to a patient in need of such treatment’ would not have a proper antecedent basis”); ’079 Patent at claims, 1, 10 (referencing “administering a single daily dose to *the patient*”) (emphasis added); *id.* at claims 5 and 14 (referencing a method “wherein the administering promotes *the patient* to sleep for 6 to 8 hours”) (emphasis added); *id.* at claims 6 and 14 (referencing a method “wherein the amount of oxybate administered to *the patient*” is of disclosed amounts) (emphasis added); ’956 Patent at claim 1 (referencing “delivering to *the patient* a formulation”); ’931 Patent at claim 1 (referencing “delivering to *the patient* a formulation”) (emphasis added).

Finally, “clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention.” *Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002). Jazz’s prosecution history shows that it relied on its preambles to distinguish its invention from the prior art. ’079 Patent File History, May 20, 2021 Remarks at 6 (distinguishing the invention from the prior art because the prior art did not “alone or in combination, teach or suggest the ... sachet’s once daily administration to treat an oxybate-treatable condition”); ’956 Patent File History, December 18, 2020 Notice of Allowance at 2 (allowing claims because “[t]he prior art does not teach or suggest, however, a method of treating cataplexy or daytime sleepiness associated with narcolepsy”); ’931 Patent File History, January 6, 2021 Notice of Allowance at 2 (allowing claims because “[t]he prior art does not teach or suggest, however, a method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy”).

b. Jazz is wrong that the “single daily dose” limitation in claims 1 and 10 of the ’079 patent does not impose any safety or efficacy requirement

Jazz’s argument that the “single daily dose” limitation of claims 1 and 10 of the ’079 patent imposes no safety or efficacy requirement also fails. Jazz’s reliance upon therapeutic efficacy “to define the claimed inventions and distinguish them from the prior art” demonstrates that the condition was “material to patentability and thus limiting.” *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1376 (Fed. Cir. 2019); *see also* ’079 Patent File History, May 20, 2021 Remarks at 8 (Jazz distinguishing its pending claims from the prior art because the prior art did not teach or suggest the “once daily administration to treat an oxybate-treatable condition”); *id.* at 11 (Jazz distinguishing its pending claims from the prior art because “when the present application was filed, it was understood in the art that oxybate required twice-daily administration to be therapeutically effective”); *id.* at 12 (Jazz distinguishing its pending claims from the prior art because “[i]n contrast, the presently-claimed methods provide therapeutic effectiveness through once daily administration”).

Additionally, the Federal Circuit has found a safety and efficacy limitation where the invention “is ultimately a formulation ([or] methods of using that formulation) that allows for increased safety and efficacy.” *Allergan Sales, LLC*, 935 F.3d at 1375. The ’079 patent is titled “GHB Formulation and Method for its Manufacture.” Its specification explains that the claimed invention includes “GHB formulations,” a “formulation of GHB designed to maintain a level of GHB in the blood,” and “controlled release and immediate release formulations [] dosed together

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to a subject to provide quick onset of action, followed by maintenance of therapeutic levels of the drug substance.” ’079 Patent at abstract, col. 4 l. 15-16, col. 4 l. 62-65. The specification of the ’079 patent thus demonstrates that Jazz believed the “efficacy and safety of the claimed methods to be material to patentability.” *Allergan Sales, LLC.*, 935 F.3d at 1375.

c. Jazz is wrong that claims 5 and 14 of the ’079 patent are non-limiting

Jazz’s expert’s opinion that dependent claims 5 and 14 of the ’079 patent are non-limiting is likewise foreclosed by Federal Circuit precedent. Where claims contain “specific requirements” and that “is all they do, and they are dependent claims,” treating those “limitations as of no legal effect would be to interpret each of these dependent claims as entirely a nullity.” *L’Oreal USA, Inc. v. Olaplex, Inc.*, 844 Fed. App’x 308, 324 (Fed. Cir. 2021). Such circumstances distinguish language from “mere statements of intended result.” *Id.* Here, dependent claims 5 and 14 contain the specific requirement of promoting patients “to sleep for 6 to 8 hours,” and contain no other limitation apart from the “wherein clause” (“wherein the administering promotes the patient to sleep for 6 to 8 hours).” ’079 Patent at claims 5, 14. It would be absurd to read such language as non-limiting.

* * *

Please confirm promptly whether Jazz agrees to withdraw the opinions identified herein. If not, please provide your availability to promptly meet and confer.

Sincerely,

/s/ Audra Sawyer

Audra Sawyer
of LATHAM & WATKINS LLP

EXHIBIT 13

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

JAZZ PHARMACEUTICALS, INC.,

Plaintiff,
v.

C.A. No. 21-691-GBW

AVADEL CNS PHARMACEUTICALS,
LLC,

Defendant.

JAZZ PHARMACEUTICALS, INC., et al.,

Plaintiffs,
v.

C.A. No. 21-1138-GBW

AVADEL CNS PHARMACEUTICALS,
LLC,

Defendant.

JAZZ PHARMACEUTICALS, INC., et al.,

Plaintiffs,
v.

C.A. No. 21-1594-GBW

AVADEL CNS PHARMACEUTICALS,
LLC,

Defendant.

REPLY EXPERT REPORT OF WILLIAM CHARMAN

[REDACTED]

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I. INTRODUCTION

1. I am the same William Charman who submitted the Opening Expert Report of William Charman, Amended Opening Expert Report of William Charman, Supplemented Opening Expert Report of William Charman, and Second Supplemented Opening Expert Report of William Charman in this litigation on behalf of Avadel CNS Pharmaceuticals, LLC (“Avadel”) on January 17, January 19, January 26, and April 28, 2023, respectively.

2. I submit this report in response to the reports of Drs. Moreton and Little, and portions of the reports of Drs. Myers and Davies, submitted on behalf of Jazz Pharmaceuticals, Inc. (“Jazz”) in this matter. For the reasons set forth below, I disagree with the opinions of Jazz’s experts, as set forth in those reports. I also incorporate my opinions set forth in my Second Supplemental Opening Report herein.

3. My opinions are set forth in this report based on my review of the reports of Jazz’s experts, the materials I have reviewed for this report (listed in Exhibit P) and my prior reports, my experience and training in the relevant field, including my experience with drug formulation and testing, and the applicable legal principles provided by counsel for Avadel.

II. BACKGROUND AND QUALIFICATIONS

4. My background, qualifications, and compensation are detailed in my Second Supplemented Opening Report, which I herein incorporate by reference.

III. CLAIM CONSTRUCTION

5. I have summarized my understanding of the Court’s definition of certain terms in the Asserted Claims of Jazz’s Patents-in-Suit in my Second Supplemented Opening Report. I have applied those definitions in responding to the opinions of Jazz’s experts. I also understand that the

the differences in the properties of non-enteric and enteric polymers, the disclosures relating to non-enteric polymers like hydroxypropyl cellulose would not enable a POSA to make and use formulations containing methacrylic acid-methyl methacrylate that achieved exhibit the claimed dissolution profile.

(3) Treatment Of Narcolepsy

166. The third point I discuss in the analysis of these *Wands* factors in my Opening Report is the need to ensure that the claimed GHB formulations have sufficient control of drug release to ensure the desired effect over the course of the night in order to treat the symptoms of narcolepsy, cataplexy, or excessive daytime sleepiness (EDS) adds a further degree of unpredictability to claimed subject matter. Charman Second Supp. Opening Rpt. ¶ 348. Dr. Moreton argues that “the Sustained Release Asserted Claims do not require efficacy in the treatment of narcolepsy and cataplexy.” Moreton Rebuttal Rpt. ¶ 126. He further opines “it is irrelevant whether there is ‘data described within the specification of the Sustained Release patents detailing a clinical effect or clinical response data of the claimed formulations’ (see Charman at ¶ 334).” Moreton Rebuttal Rpt. ¶ 126. For the reasons previously discussed, I disagree with Dr. Moreton’s views. *Supra* § IV.A.9. It is my opinion that a POSA seeking to make or use the claimed GHB formulations in the Sustained Release patents would understand that the claims as construed by the Court cover GHB formulations suitable for the once-nightly treatment of narcolepsy. Charman Second Supp. Opening Rpt. ¶ 326. As already noted, this is consistent with both Jazz’s representations in this case to date, and with Mr. Allphin’s declarations to the USPTO during the prosecution of the ’488 patent. *Supra* ¶ 118.

(4) Oral Administration Of The Formulation

specification of the Resinate patents do by stating that “[o]ne object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours” (i.e., a full night’s sleep). *See* ’079 patent at 4:4-14. In my opinion, a POSA would read the claims as requiring that the claimed method result in safe and effective treatment of narcolepsy, cataplexy, and excessive daytime sleepiness via administration of a single daily dose of oxybate. And at the very least, a POSA reading the claims would view the preambles of claims 1 and 10 of the ’079 patent as requiring administering the claimed formulations for the purpose of treating narcolepsy (claim 1) or cataplexy or excessive daytime sleepiness (claim 10). Thus, the preambles of claim 1 and 10 recite an intended purpose or method to be performed in someone in need, and would therefore be considered by a POSA reading them to be limitations to the claims.

279. Claims 1 and 10 of the ’079 patent also recite “administering a single daily dose to the patient.” I do not agree with Dr. Little’s opinion that this limitation “requires only that one dose per day be administered”, but not to any specific end. Little Rebuttal Rpt. ¶ 51. Dr. Little recites his understanding from counsel that “if the steps of ‘method of treating’ claims are carried out the same way, regardless of whether the purpose or intended result is achieved, then there is no safety or efficacy requirement in the claims.” Little Rebuttal Rpt. ¶ 51. That is, according to Dr. Little, the claims are practiced as long as the single daily dose is administered in the manner recited, i.e., by opening a sachet, mixing the formulation with water, and orally administering the mixture. *Id.* I do not agree with Dr. Little’s opinions, which are based on his understanding of legal principles supplied by Jazz’s counsel. Based on my understanding of legal principles described by Avadel’s counsel, I do not believe a POSA would read the claims in a way that gives no effect to the requirement that the claimed formulation is administered as a single daily dose. Instead, I believe that a POSA would have understood the claim language “administering a single

daily dose to the patient” to reflect a requirement that the single dose administered be considered safe and effective at treating narcolepsy and/or cataplexy or excessive daytime sleepiness, and at the very least that it can be administered in that manner for the recited purpose of treating narcolepsy and/or cataplexy or excessive daytime sleepiness. Moreover, as I describe in greater detail below, under Dr. Little’s interpretation of the claims as well as my own (as informed by counsel) the claims require a level of safety that at least permits administration to a patient. If the claimed formulation is to be administered to a patient at all, that indicates that it must be safe for human ingestion.

280. Again, this is particularly true given the specification’s indication that the purpose of the invention is to provide once-nightly dosing, and the applicant’s arguments during prosecution of the ’079 patent that the once-nightly feature of the claims distinguished them over the prior art (which only described twice-nightly dosing). For example, I have reviewed an Office Action Response in the ’079 patent file history where Jazz argued that the invention was distinguished over the prior art because the prior art did not “provide a rationale to administer a *single daily dose* of a solid oxybate formulation to the patient from a sachet.” Ex. M (’079 patent File History, Office Action Response at 11 (May 20, 2021)(emphasis in original). Jazz argued that this “*deficiency is particularly relevant* because, when the present application was filed, it was understood in the art that oxybate required twice-daily administration to be therapeutically effective....Therefore, none of the cited references suggests the claim-recited *single daily administration* of a solid oxybate formulation dispensed from a sachet to treat an oxybate-treatable condition.” *Id.* at 11-12. Indeed, Jazz made clear that “the presently-claimed methods provide *therapeutic effectiveness through once-daily administration.*” *Id.* at 12. Thus, the prosecution history demonstrates that Jazz believed the preambles of claims 1 and 10 to be limiting, and to

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

30 June 2023
Date

William Charman
William N. Charman

EXHIBIT 14

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

JAZZ PHARMACEUTICALS, INC.,

Plaintiff,

v.

C.A. No. 21-691-GBW

AVADEL CNS PHARMACEUTICALS,
LLC,

Defendant.

JAZZ PHARMACEUTICALS, INC., et al.,

Plaintiffs,

v.

C.A. No. 21-1138-GBW

AVADEL CNS PHARMACEUTICALS,
LLC,

Defendant.

JAZZ PHARMACEUTICALS, INC., et al.,

Plaintiffs,

v.

C.A. No. 21-1594-GBW

AVADEL CNS PHARMACEUTICALS,
LLC,

Defendant.

SECOND SUPPLEMENTAL OPENING EXPERT REPORT OF ROBERT S. LANGER

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I. INTRODUCTION

1. My name is Dr. Robert S. Langer. I am currently an Institute Professor (one of twelve Institute Professors, the highest rank awarded to a faculty member) at the Massachusetts Institute of Technology (MIT). My appointments include those in the Department of Chemical Engineering at MIT, the Department of Biological Engineering, the Institute for Medical Engineering and Science, and the Harvard-MIT Division of Health Sciences and Technology.

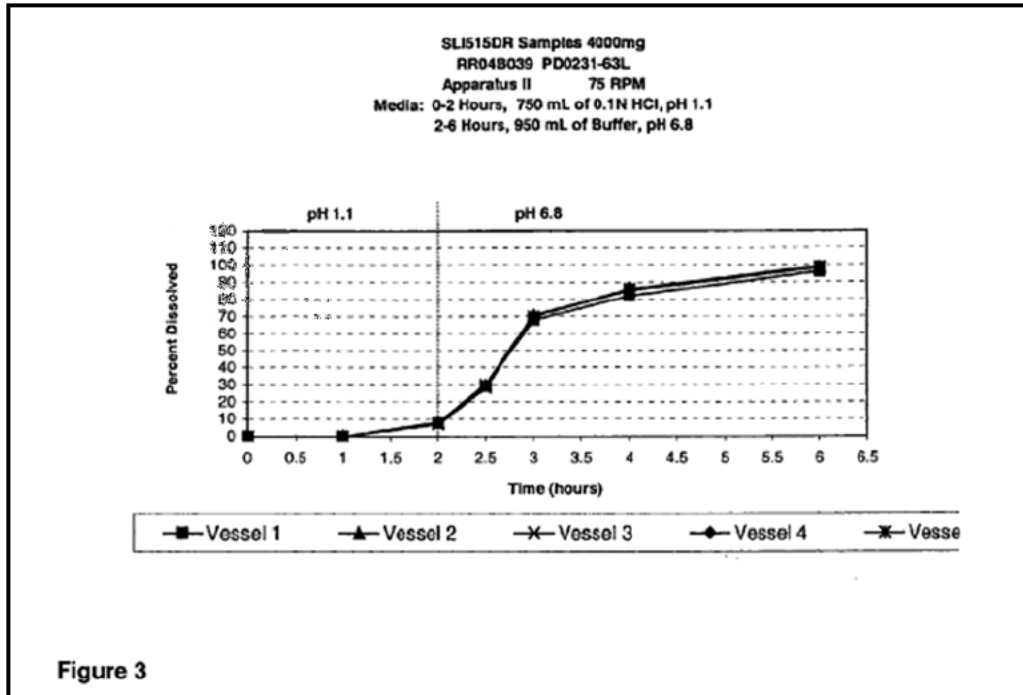
2. I have been retained on behalf of Avadel CNS Pharmaceuticals, LLC (“Avadel”) who I understand to be the defendant in the patent litigations identified in the caption of this report, to provide my opinions regarding the validity of certain claims of U.S. Patent Nos. 10,758,488 (the “’488 patent”); 10,813,885 (the “’885 patent”); 10,959,956 (the “’956 patent”); and 10,966,931 (the “’931 patent”) (collectively, the “Sustained Release Patents”).

3. My opinions are based on my review of relevant documents and information, my experience in the fields of pharmaceutical development and drug delivery, particularly as applied to pharmaceutical products, and my understanding of the relevant legal framework as explained to me by counsel for Avadel.

II. SCOPE OF THE REPORT

4. This report sets forth the opinions as to which, if asked, I will testify at trial with respect to the validity of the Sustained Release Patents.

5. Counsel informed me that Jazz has asserted the following claims from its Sustained Release Patents: claims 1-12 of the ’488 patent; claims 1-15 of the ’885 patent; claims 1-20 and 23-25 of the ’956 patent; claims 1-15 of the ’931 patent (collectively, the “Asserted Claims of the Sustained Release Patents”). Therefore, I have only provided my opinions as to the Asserted Claims of the Sustained Release, but I can provide opinions and analysis of the remaining claims of the Sustained Release if called upon to do so.



B. The Asserted Claims of the Sustained Release Patents Are Anticipated by Liang 2006

50. I have not opined on whether the Asserted Claims of the Sustained Release Patents are adequately described or enabled by the Sustained Release Patents. However, I have been instructed by counsel to assume for the sole purpose of the analysis below that the Asserted Claims of the Sustained Release Patents are adequately described and enabled by the Sustained Release Patents. I have no opinion with respect to the correctness of that instruction. In view of this instruction and my analysis below, the Asserted Claims of the Sustained Release Patents would have been anticipated by Liang 2006. I have attached Appendix D showing the disclosure of each limitation of the Asserted Claims of the Sustained Release Patents in Liang 2006.

1. Preamble

51. The preamble of claim 1 of the '488 patent is representative of the preambles for the Asserted Claims of the Sustained Release Patents: "A formulation comprising immediate release and sustained release portions, each portion comprising at least one pharmaceutically active

ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate.”

52. Because Liang 2006 teaches an oral pharmaceutical dosage form of GHB “comprising an immediate release component of gamma-hydroxybutyric acid (GHB), and one or more delayed/controlled release components of gamma-hydroxybutyric acid,” Liang 2006, at claim 1, the preamble is disclosed in Liang 2006 to the extent it is limiting.

2. Immediate Release Claim Limitation

53. Claim 1(b) of the '488 patent is representative of the Asserted Claims of the Sustained Release patents:

b. the immediate release portion comprises about 75% and about 98% by weight of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, and the amount of gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the immediate release portion is about 10% to 50% by weight of the gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the formulation;

54. Liang 2006 discloses that “[t]he immediate release component comprises from about 20% to about 100% by weight of one or more gamma-hydroxybutyric acid salts and optionally one or more pharmaceutically acceptable excipients.” Liang 2006 at ¶ 52. Further, “the immediate release dose can be equivalent of, higher than, or lower than, the one or more delayed release doses.” *Id.* at ¶ 39. Thus, a POSA would understand Liang 2006 to disclose the immediate release particle limitations.

3. Dosing Range Limitation

55. Claim 12(a) of the '488 patent is representative of this type of limitation. It additionally requires that the immediate release portion “comprises about 55 mg to 12 g of at least one pharmaceutically active ingredient.”

Dated: July 18, 2023


Dr. Robert S. Langer

EXHIBIT 15

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

JAZZ PHARMACEUTICALS, INC.,

Plaintiff,

v.

C.A. No. 21-691-GBW

AVADEL CNS PHARMACEUTICALS,
LLC,

Defendant.

JAZZ PHARMACEUTICALS, INC., et al.,

Plaintiffs,

v.

C.A. No. 21-1138-GBW

AVADEL CNS PHARMACEUTICALS,
LLC,

Defendant.

JAZZ PHARMACEUTICALS, INC., et al.,

Plaintiffs,

v.

C.A. No. 21-1594-GBW

AVADEL CNS PHARMACEUTICALS,
LLC,

Defendant.

SECOND SUPPLEMENTAL OPENING EXPERT REPORT OF
ALEXANDER M. KLIBANOV, PH.D.

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I. QUALIFICATIONS

1. I, Alexander M. Klibanov, Ph.D., expect to testify on behalf of the Defendant Avadel CNS Pharmaceuticals, LLC (“Avadel”) in the above-captioned litigation against Plaintiffs Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited (together, “Jazz”) as an expert witness regarding the validity of certain claims of U.S. Patent Nos. 11,077,079 (the “’079 Patent”) and 11,147,782 (the “’782 Patent”).

2. I am currently a Professor Emeritus of Chemistry and Bioengineering at the Massachusetts Institute of Technology (“M.I.T.”), where I taught and conducted research for over 40 years. From 2014 to 2019 (and also from 2007 to 2012), I held the Novartis Endowed Chair Professorship at M.I.T. From 2012 to 2014, I held the Roger and Georges Firmenich Endowed Chair Professorship in Chemistry. Prior to that, I was a Professor of Chemistry and a Professor of Bioengineering at M.I.T., positions I held from 1988 and 2000, respectively. From 1979 to 1988, I was an Assistant Professor, then Associate Professor, and thereafter a Full Professor of Applied Biochemistry in the Department of Applied Biological Sciences (formerly the Department of Nutrition and Food Science) at M.I.T.

3. I obtained my M.S. degree in Chemistry from Moscow University in Russia in 1971 and my Ph.D. in Chemical Enzymology from the same University in 1974. Thereafter, I was a Research Chemist at Moscow University’s Department of Chemistry for three years. From 1977 to 1979, following my immigration to the United States, I was a Post-Doctoral Associate at the Department of Chemistry, University of California in San Diego.

4. Over the last 50+ years as a practicing chemist, I have extensively researched, published, taught, and lectured in many areas of chemistry, including biological, pharmaceutical formulation, general, and medicinal.

adequate written description support in, or are enabled by, the '079 Patent specification. Instead, for purposes of this report, I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '079 Patent specification identified in Jazz's Final Validity Contentions. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '079 Patent, and (b) the '079 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the '079 Patent. As explained above, I have also been instructed to assume, for my analysis in this report, that Jazz is correct that the claimed oxybate/gamma-hydroxybutyrate formulations can encompass sodium oxybate formulations. My opinions herein are premised on that assumption (with which I disagree). Notably, I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

44. I have also reviewed Jazz's Final Validity Contentions that the Asserted Claims of the '079 Patent are not obvious. *See* Jazz's Final Validity Contentions at 105-49. Based on my review, I understand that Jazz only disputes whether the following two claim limitations of the Asserted Claims of the '079 Patent would have been non-obvious: "opening a sachet containing an oxybate formulation" and "mixing the formulation with water." *Id.* at 138-49.

1. Claim 1

a. "A method of treating narcolepsy in a patient in need thereof, the method comprising:"

45. To the extent that this preamble is limiting (i.e., acts as a claim limitation), it is my opinion that a POSA would have found that both Liang 2006 and Lebon 2013 disclose "[a] method of treating narcolepsy in a patient in need thereof." I note that Jazz does not challenge the

obviousness of this claim preamble in its Final Validity Contentions. Jazz’s Final Validity Contentions at 138-49.

46. Liang 2006 discloses that sodium gamma-hydroxybutyrate, which Liang abbreviates as “GHB” can be used “in the treatment of narcolepsy.” *Id.* at ¶ 1; *see also id.* at ¶ 2 (“Sodium gamma-hydroxybutyrate (GHB or sodium oxybate) . . . has broad indications including narcolepsy.”); ¶ 5 (“Xyrem® is prescribed to narcolepsy patients.”). Lebon 2013 similarly discloses that Xyrem (sodium oxybate), “is used for the treatment of narcolepsy in adult patients exhibiting cataplexy.” *Id.* at col. 1, ll. 28-31. But Lebon 2013 explains that “the major drawback of GHB in terms of effectiveness is linked to its pharmacokinetic profile,” limiting the effectiveness of GHB and requiring the administration of multiple doses repeated every few hours. *Id.* at col. 1, ll. 36-52. Lebon 2013 states that the “object of the present invention” was to provide a “novel galenic form based on gamma-hydroxybutyric acid or one of its salts (in particular sodium) which makes it possible to circumvent the aforementioned drawbacks” associated with the administration of GHB. *Id.* at col. 1, ll. 64-67.

47. Since this preamble was disclosed by both Liang 2006 and Lebon 2013, a POSA would have found this claim preamble to be obvious.

b. “(a) administering a single daily dose to the patient”

48. I note that Jazz does not challenge the obviousness of this claim limitation in its Final Validity Contentions. Jazz’s Final Validity Contentions at 138-49.

49. I have reviewed Jazz’s Final Validity Contentions as to whether the “administering a single daily dose to the patient” claim limitation has written description support in, and is enabled by, the ’079 Patent specification. *See* Jazz’s Final Validity Contentions at 203-06.

50. I have not been asked to consider whether this claim limitation indeed has adequate written description support in, or is enabled by, the ’079 Patent specification. Instead, for purposes

of this report, I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '079 Patent specification identified by Jazz. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '079 Patent, and (b) the '079 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the '079 Patent. I have also been instructed to assume that the claims encompass administration of oxybate salt formulations (*i.e.*, salts of oxybate or, more precisely, salts of gamma-hydroxybutyric acid). Notably, I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

51. In view of these instructions, I have concluded that the subject matter of the Asserted Claims of the '079 Patent would have been obvious to a POSA as of the priority date, including that a POSA would have been motivated to achieve a single daily dose of GHB as claimed with a reasonable expectation of success in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. That analysis is set forth below.

52. Liang 2006 describes a single daily dosage of GHB that is convenient because "a patient does not need to wake up and take a second dose during the night." Liang 2006 at ¶ 36. Liang 2006 discloses a way to achieve a "single daily dose" by combining immediate release and "delayed/controlled release particles" of GHB, which it teaches "can constitute a complete once-nightly or once-daily dose." *Id.* at ¶ 32. Liang 2006 clarifies that the term "combining" can mean supplying and consuming all components "simultaneously in the same presentation or dosage form." *Id.* Liang 2006 further discloses that the "delayed/controlled release" particles and

immediate release component can be “supplied as pre-mixed doses,” thus comprising a single dosage. *Id.* at ¶ 33.

53. Likewise, Lebon 2013 teaches that its invention “reduce[s] . . . the number of times it [i.e., gamma-hydroxybutyric acid or its salt] is taken per day.” *Id.* at col. 2, ll. 1-4. Lebon 2013 further describes the current dosing regimen for narcolepsy as “repeated every 3 to 4 hours. . . in the middle of the night.” *Id.* at col. 1, ll. 46-48.

54. Based on the disclosures in Liang 2006 and Lebon 2013, and given the aforementioned assumption that the ’079 Patent has adequate written description and enablement for this claim limitation, a POSA would have been motivated to achieve a method of administering a single daily dose to a patient with a reasonable expectation of success.

55. I have also reviewed, and rely on, the opinion of Bruce Corser, M.D., who opined that, as of 2010, physicians specializing in sleep recognized shortcomings of twice-nightly forms of oxybate, and consequently recognized the need for once-nightly forms of oxybate. *See* Corser Report at ¶¶ 56-65.

56. Thus, it is my opinion that a POSA would have found this claim limitation to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

c. “(b) the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate,”

57. In light of the assumptions I have been instructed to make, this claim limitation would have been obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge available to a POSA. Liang 2006 and Lebon 2013 both disclose “an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate.” I note that Jazz does not challenge the obviousness of this claim limitation in its Final Validity Contentions. Jazz’s Final Validity Contentions at 138-49.

4. Claim 5

a. “The method of claim 1, wherein the administering promotes the patient to sleep for 6 to 8 hours.”

103. Claim 5 depends directly on claim 1 and further recites “wherein the administering promotes the patient to sleep for 6 to 8 hours.” Jazz does not separately challenge the obviousness of this claim limitation. Jazz’s Final Validity Contentions at 138-49.

104. I have reviewed Jazz’s Final Validity Contentions as to whether the “wherein the administering promotes the patient to sleep for 6 to 8 hours” claim limitation has written description support in, and is enabled by, the ’079 Patent specification. *See* Jazz’s Final Validity Contentions at 96-98. Jazz contends that the written description legal requirement is satisfied because: “One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours. . . . Additionally, it is an object of the invention to ensure that the sleep inducing effects of GHB do not remain for longer than the above periods as it would compromise a patient’s ability to perform normal day to day activities.” (’079 Patent at col. 4, ll. 4-13). *Id.* at 96.

105. I have not been asked to consider whether this claim indeed has adequate written description support in, or is enabled by, the ’079 Patent specification. Instead, for purposes of this report, I have been instructed by Counsel to take as true Jazz’s contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the ’079 Patent specification identified by Jazz. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the ’079 Patent, and (b) the ’079 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the ’079 Patent. I have also been instructed to assume that the

asserted claims may be satisfied by administration of a solid formulation of oxybate salts. Notably, I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

106. In view of these instructions, I have concluded that the subject matter of the Asserted Claims of the '079 Patent would have been obvious to a POSA as of the priority date, including that a POSA would have been motivated to arrive at a formulation that promotes a patient to sleep for 6 to 8 hours with a reasonable expectation of success.

107. Liang 2006 discloses administering the dosage form so as to promote the patient to sleep for 6 to 8 hours. It teaches that the twice-nightly Xyrem solution was inconvenient because it required that the patient wake up after 4 hours to take a second dose. Liang 2006 at ¶ 3 (“Patients take an initial dose of sodium gamma-hydroxybutyrate around bedtime and must wake up four hours later to take a second dose. . . . Such a dose regimen is rather inconvenient.”). A POSA would have therefore understood that it is desirable to arrive at a formulation that promotes a total of approximately eight hours of sleep with a single daily dose.

108. As discussed above, Jazz contends that written description is satisfied because: “One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours. . . . Additionally, it is an object of the invention to ensure that the sleep-inducing effects of GHB do not remain for longer than the above periods as it would compromise a patient’s ability to perform normal day to day activities.” ('079 Patent at col. 4, ll. 4-13). Jazz’s Final Validity Contentions at 96. The disclosure in Liang 2006 is substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the '079 Patent.

109. Lebon 2013 provides a similar motivation. It teaches that the narcoleptic patient needed to take a commercially existing dose of sodium GHB every 3-4 hours in the middle of the night. *Id.* at col. 1, ll. 46-49. A POSA would have understood the disclosure in Lebon 2013 to mean that each dose of Xyrem only caused the patient to sleep for 3-4 hours per dose. *See* Xyrem 2014 Label at 3 (instructing patients to take the first dose at bedtime and the second dose 2.5 to 4 hours later).

110. As discussed above, Jazz contends that written description is satisfied because: “One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours. . . . Additionally, it is an object of the invention to ensure that the sleep inducing effects of GHB do not remain for longer than the above periods as it would compromise a patient’s ability to perform normal day to day activities.” (’079 Patent at col. 4, ll. 4-13). Jazz’s Final Validity Contentions at 96. The disclosure in Lebon 2013 is substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the ’079 Patent.

111. Further, it was well known in the art at the priority date of the ’079 Patent that 6 to 8 hours of sleep per night was considered optimal for patients taking sodium oxybate. For example, Mignot provides a review of methods of administering sodium oxybate to narcolepsy patients so that the patient can “fully consolidate a six to eight hour night.” Emmanuel J. M. Mignot, *A Practical Guide to the Therapy of Narcolepsy and Hypersomnia Syndromes*, 9 NEUROTHERAPEUTICS 739, 746 (2012). Thus, Mignot would have provided a POSA with further motivation to promote the patient to sleep for 6 to 8 hours.

112. Given the aforementioned assumption that the ’079 Patent has adequate written description and enablement for this claim limitation, both Liang 2006 and Lebon 2013 would have

provided a POSA with the motivation and a reasonable expectation of success in obtaining such a dosage form. *See* Liang 2006 at ¶ 12 (“It provides a convenient once nightly or once daily dose regiment for the oral delivery of one or more gamma-hydroxybutyric acid salts to an animal.”), ¶ 32 (“Combining the immediate release component and one or more pH sensitive delayed/controlled release particles of the current invention can constitute a complete once-nightly or once-daily dose.”); ¶ 33 (clarifying “delayed/controlled release” particles and immediate release component can be “supplied as pre-mixed doses,” thus comprising a single dosage); Lebon 2013 at col. 2, ll. 1-4 (“Thus an object of the present invention is to provide a novel galenic form based on gamma-hydroxybutyric acid or one of its salts which makes it possible to reduce the daily dose and the number of times it is taken per day...”).

113. Therefore, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

5. Claim 6

- a. **“The method of claim 1, wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.”**

114. Claim 6 depends directly on claim 1 and further recites “wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.” Jazz does not separately challenge the obviousness of this claim limitation. Jazz’s Final Validity Contentions at 138-49.

115. In light of the assumptions I have been instructed to make, it is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

Dated: April 28, 2023


Alexander M. Klibanov, Ph.D.